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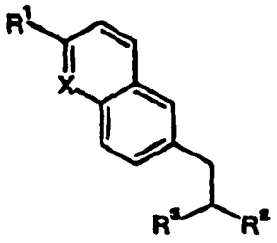
(54) Title: 2,6-QUINOLINYL AND 2,6-NAPHTHYL DERIVATIVES, PROCESSES FOR PREPARING THEM AND THEIR USES AS VLA-4 INHIBITORS



(I)

(57) Abstract: The present invention concerns 2,6-quinolinyl and 2,6-naphthyl derivatives of formula (I), processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals for the treatment of VLA-4 dependent inflammatory diseases such as for example asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and atherosclerosis. Formula (I): wherein X is N or CH.

2,6-QUINOLINYL AND 2,6-NAPHTHYL DERIVATIVES, PROCESSES FOR PREPARING THEM AND THEIR USES AS VLA-4 INHIBITORS

The present invention concerns 2,6-quinolinyl and 2,6-naphthyl derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

During the inflammatory process white blood cells infiltrate the extravascular tissue.

This recruitment into areas of inflammation involves the binding of leukocytes to endothelium followed by their transmigration into the tissue. Each step of this process is mediated by specific interactions between adhesion molecules present on the leukocyte cell surface and their counter-ligands expressed on vascular endothelium, epithelium and matrix proteins (B.S. Bochner in Allergy Principles and Practice, E. Middleton et al, Eds. St Louis: Mosby, 1998, 94-107).

Adhesion molecules expressed on leukocytes can be sub-divided into different groups according to their structures. The two principal groups are the selectin family or their ligands and the integrin family. The different patterns and levels of the expression of these molecules on different leukocyte subsets may explain, to some extent, the differential pattern of leukocyte recruitment in inflamed tissues (B.S. Bochner et al., Immunological Reviews (2001), 179, 5-15).

During the initial step of migration from the blood, leukocytes undergo tethering and rolling, which are principally mediated by the interaction of selectins with their carbohydrated counter-ligands. It has been reported that for some leukocytes, especially eosinophils, the interaction of the $\alpha 4\beta 1$ integrin with its endothelial ligand stabilizes rolling and enhances the cell's arrest (J. Kitayama, J. Immunol. (1997),159, 3929-3939).

The following firm adhesion to endothelium and cell spreading are mediated by leukocyte integrin interaction with immunoglobulin super-family molecules expressed on the activated endothelium. This step requires leukocyte activation by chemo-attractants or other factors produced in close proximity to the endothelium or by direct interaction with it. Such activation leads to an increase in affinity and/or expression of the integrin resulting in an increased binding to endothelial counter-ligands. Rapid and reversible up-regulation of these molecules allows cells to adhere, detach and migrate.

Leukocytes subsequently transmigrate to the tissue, a process which is also influenced by the interaction of integrins with their endothelial ligands.

Once in the extravascular compartment cells may remain tissue resident, a process maintained by integrin interaction with matrix proteins. Cells may also undergo apoptosis, a process that may be inhibited by integrin/matrix protein interaction (A.R.E. Anwar et al, J. Exp. Med. (1993), 177, 839-843).

Integrins are hetero-dimeric membrane glycoproteins composed of non-covalently associated α and β subunits in combinations that determine ligand specificity. So far 15 α and 8 β chains have been identified and 13 different integrins are expressed on leukocytes. Sub-families β1, β2 and β7 are involved in cell adhesion to endothelium.

The integrin α4β1 (also termed VLA-4 or Very Late Antigen-4 and designated CD49d/CD29) is predominantly expressed on eosinophils, lymphocytes, monocytes and basophils. It binds primarily to the vascular cell surface adhesion molecule VCAM-1 that is expressed on endothelium in response to inflammatory cytokines (TNF-α, IL-1 and selectively IL-4 and IL-13) and to the extracellular matrix protein fibronectin.

Because VLA-4 is not expressed on circulating neutrophils, which are the first defense against infection, it is an attractive target for the pharmacological control of inflammatory diseases.

Several studies have shown that VLA-4 is involved in allergic diseases such asthma and that blocking its function is beneficial.

Asthma is characterized by the accumulation of eosinophils and lymphocytes in bronchial tissue. Immuno-histological analysis of bronchial sub-mucosa obtained from asthmatic patients revealed that VLA-4 is strongly expressed in infiltrated eosinophils and T lymphocytes (V. Bocchino et al, Allergy Clin. Immunol. (2000), 105, 65-70; K. Tomita, Clin. Exp. Allergy (1997), 27, 664-671; Y. Okhawara, Am. J. Respir. Cell Mol. Biol. (1995), 12, 4-12). Over-expression of VCAM-1 was reported in bronchial biopsies from allergic asthmatics compared to normals (P. Gosset et al, Int. Arch. Allergy Immunol. (1995), 106, 69-77). Allergen challenge experiments have shown that several adhesion molecules, including VCAM-1, are up-regulated following the exposure and that this increased expression is correlated with eosinophil infiltration into the tissue space (J. Zangrilli et al, Am. J. Respir. Crit. Care Med. (1995), 151, 1346-1353; T. Fukuda, Am. J. Respir. Cell Mol. Biol. (1996), 14, 84-94).

In several animal models of allergic asthma, blockade of VLA-4 with monoclonal antibody has been shown to reduce the numbers of eosinophils and lymphocytes in the broncho-alveolar fluid (BAL). Some experiments have shown that, in guinea pigs and rats, treatment with a VLA-4 monoclonal antibody inhibits either the late phase response or the airway hyperreactivity seen in these models with a concomitant decrease in eosinophil accumulation in the bronchial tissue (M. Protelani, J. Exp. Med. (1994), 180, 795-805; H.A. Rabb et al, Am. J. Respir. Crit. Care Med. (1994), 149, 1186-1191; H. Sagara, Int. Arch. Allergy Immunol. (1997), 112, 287-294). In a sheep model, VLA-4 monoclonal

antibody inhibited the late phase response with a modest reduction in the number of BAL eosinophils (W.M. Abraham et al, J. Clin. Invest. (1994), 93, 776-787). In a mouse model of allergic asthma, intrapulmonary blockade of VLA-4 decreased hyperresponsiveness and Th2 cytokine release whereas VLA-4 blockade on circulating leukocytes decreased the number of eosinophils in BAL fluid (W.R. Henderson et al, J. Clin. Invest. (1997), 100, 3083-3092).

Consistent with these observations, VCAM deficient mice failed to develop pulmonary eosinophilia following ovalbumin challenge (J.-A. Gonzalo et al, J. Clin. Invest. (1996), 10, 2332-2345).

Several in vitro and in vivo studies have indicated an important role of VLA-4 in other cell adhesion-mediated inflammatory pathologies including multiple sclerosis (MS), rheumatoid arthritis (RA), atherosclerosis or inflammatory bowel disease.

Inhibition of VLA-4 function using monoclonal antibodies in a variety of inflammation animal models has proved to be beneficial (R.R. Lobb, J. Clin. Invest. (1994), 94, 1722-1728).

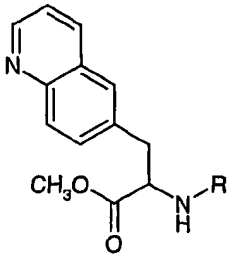
Migration of T lymphocytes into the central nervous system is an important event in the pathogenesis of multiple sclerosis. The VCAM-1/VLA-4 adhesion pathway appears to be of key importance (B. Cannella et al, Ann-Neurol. (1995), 37, 424-435; I. Elovaara et al, Arch-Neurol. (2000), 57, 546-551; S. Lujan et al, Mult-Scler. (1998), 4, 239-242). In a model of experimental allergic encephalomyelitis, which mimics MS, treatment with a monoclonal antibody against VLA-4 decreased both clinical and histopathological parameters (E. Keszthelyi et al, Neurology (1996), 47, 1053-1059).

Rheumatoid arthritis is characterized by infiltration of mononuclear cells into the synovial tissue. Interaction of VLA-4 with VCAM-1 and with the alternative spliced fibronectin containing the CS1 region is thought to mediate the recruitment, the retention and the activation of VLA-4-bearing cells in the inflamed joints (P.P. Sfikakis, Clin. Rheumatol. (1999), 18, 317-327). Treatment with a monoclonal antibody against VLA-4 significantly reduced oedema formation in an animal model of polyarthritis (which shares features with RA (A. Inaro, Lab. Invest. (2000), 80, 73-80)) and inflammatory cell tissue infiltration in the inflamed rat knee joint capsule (V. Finkenauer, Microcirculation (1999), 6, 141-152).

Treatment with a anti-α4 monoclonal antibody has a beneficial effect in cotton top tamarin model of colitis (D.K. Podolsky, J. Clin. Invest. (1993), 92, 372-380).

Specific inhibitors of the VLA-4 interaction with its ligands VCAM-1 or fibronectin may be effective in the treatment of asthma and other inflammatory disorders.

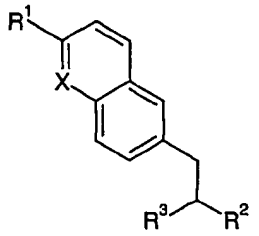
The international patent application WO0015612-A1 teaches compounds having a general formula



wherein R represents some substituents such as hydrogen, -COOH, -COOalkyl. These compounds can be used as intermediate compounds in a preparation of pharmaceutical compounds, but no pharmaceutical utility for them as such is sought.

It has now surprisingly been found that some analogs of these compounds demonstrate therapeutic properties.

In one aspect, the invention therefore provides a compound having the formula I or a pharmaceutically acceptable salt thereof,

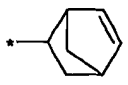


(I)

wherein

X is N or CH;

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or an oxy derivative, or a group of formula:

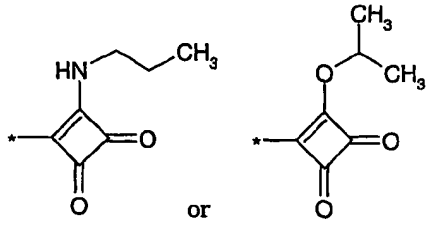


;

R^2 is $-NR^4R^5$, $-OR^4$ or $-C(=O)NR^5R^6$;

R^3 is tetrazole, -CN, $-CH_2OH$ or $-CO-R^7$;

R^4 is H, $-G^1-R^8$, or a group of formula:



;

R^5 is H, C1-4-alkyl; or $-NR^4R^5$ represents an heterocycle or $-N=CR^9R^{10}$;

R^6 is aryl, heterocycle, cycloalkyl or aralkyl;

R^7 is hydroxy, amino, hydroxylamino, an oxy derivative or an amino derivative;

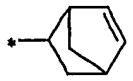
G^1 is CO, CH_2, SO_2;

R^8 is aryl, heterocycle, cycloalkyl, aralkyl or -NH-aryl;

R^9 is aryl; and

R^{10} is ether;

with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:



; and

with the proviso that, when X is CH, R^1 is cycloalkyl, R^2 is $-NR^4R^5$, R^3 is $-CO-R^7$, R^4 is H or $-G^1-R^8$, R^5 is H, C1-4-alkyl, G^1 is CO, CH_2, SO_2, R^8 is an optionally substituted phenyl, cycloalkyl or -NH-phenyl (an optionally substituted), then R^7 is neither an oxy derivative of formula $-O-CHR^bR^c$ wherein R^b is H, C1-6-alkyl or an optionally substituted phenyl and R^c is an optionally substituted phenyl, nor an amino derivative of formula $-NR^d-CHR^bR^c$ wherein R^b and R^c have the same definitions as described above, and R^d is H or C1-6-alkyl.

In the definitions set forth below, unless otherwise stated, the term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-8 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl") and includes alkyl moieties substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, acyl derivative, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, esteroxy, amidooxy, heterocycle, vinyl, C1-6-alkoxy, C6-10-aryloxy and C6-10-aryl.

Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, iso- or tert-butyl, and 2,2-dimethylpropyl each optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro and cyano, such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

The term "cycloalkyl", as used herein, refers to a monovalent group of 3 to 18 carbons derived from a saturated cyclic or polycyclic hydrocarbon such as adamantyl,

which can optionally be substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl or other groups as described above for the alkyl groups. Non-limiting examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, bicyclo[3.2.1]cyclooctanyl or adamantyl.

The term "alkenyl" as used herein, is defined as including branched, unbranched and cyclic unsaturated hydrocarbon radicals having at least one double bond such as ethenyl (= vinyl), 1-methyl-1-ethenyl, 2-methyl-1-propenyl, 1-propenyl, 2-propenyl (= allyl), 1-butenyl, 2-butenyl, 3-butenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 1-hexenyl, 2-hexenyl, and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle such as mono- and di-halo vinyl where halo is fluoro, chloro or bromo.

The term "alkynyl" as used herein, is defined as including monovalent branched, unbranched and cyclic hydrocarbon radicals containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl (= propargyl), and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle, such as haloethynyl.

When present as bridging groups, alkyl, alkenyl and alkynyl represent straight or branched chains, C1-12-, preferably C1-4-alkylene or C2-12-, preferably C2-4-alkenylene or -alkynylene moieties respectively.

Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e.g. "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.

The term "aryl" as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl derivative, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, C1-6-alkyl, C1-6-haloalkyl, C3-8-cycloalkyl, sulfonic acid, sulfonamide, thio derivative, esteroxy, amidooxy, heterocycle, vinyl, C1-6-alkoxy, C6-10-aryloxy or C6-10 aryl, where two or more substituents may form a ring attached to the aryl moiety. Preferred aryl groups are phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl and phenyl.

The term "aralkyl", as used herein, represents a group of the formula -R^{13}-aryl in which R^{13} is C1-12- straight, branched or cyclic alkylene, or C2-12- straight or branched alkenylene or alkynylene groups. Non-limiting examples are benzyl, halobenzyl, cyanobenzyl, methoxybenzyl, nitrobenzyl, 2-phenylethyl, diphenylmethyl, (4-methoxyphenyl)diphenylmethyl, anthracenylmethyl.

The term "halogen", as used herein, includes a Cl, Br, F or I atom.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "thiol", as used herein, represents a group of the formula -SH.

The term "cyano", as used herein, represents a group of the formula -CN.

The term "nitro", as used herein, represents a group of the formula -NO_2.

The term "amino", as used herein, represents a group of the formula -NH_2.

The term "hydroxylamino", as used herein, represents a group of the formula -NHOH.

The term "azido", as used herein, represents a group of the formula -N_3.

The term "carboxy", as used herein, represents a group of the formula -COOH.

The term "sulfonic acid", as used herein, represents a group of the formula -SO_3H.

The term "sulfonamide", as used herein, represents a group of the formula -SO_2NH_2.

In the definitions set forth below, unless otherwise stated, R^{11} and R^{12} are the same or different and each is independently amido, alkyl, alkenyl, alkynyl, acyl, ester, ether, aryl, aralkyl, heterocycle, heterocycle-alkyl, or an oxy derivative, thio derivative, acyl derivative, amino derivative, sulfonyl derivative, or sulfinyl derivative, each optionally substituted with any suitable group, including, but not limited to, one or more moieties selected from lower alkyl or other groups as described above as substituents for alkyl.

The term "ester" as used herein is defined as including a group of formula -COO-R^{11a} wherein R^{11a} is as defined above for R^{11} except for "oxy derivative", "thio derivative" or "amino derivative".

The term "ether" is defined as including a group selected from C1-50- straight or branched alkyl, or C2-50- straight or branched alkenyl or alkynyl groups or a combination of the same, interrupted by one or more oxygen atoms.

The term "amido" is defined as including a group of formula -$CONH_2$ or -$CONHR^{11b}$ or -$CONR^{11b}R^{12a}$ wherein R^{11b} and R^{12a} are as defined above for R^{11} and R^{12}.

The term "oxy derivative", as used herein is defined as including -O-R^{11c} groups wherein R^{11c} is as defined above for R^{11} except for "oxy derivative", "thio derivative" and

"amino derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, esteroxy, amidooxy, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocyclooxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyloxy, 2-pyridyloxy, methylenedioxy, carbonate.

The term "thio derivative", as used herein, is defined as including -S-R^{11d} groups wherein R^{11d} is as defined above for R^{11} except for "thio derivative", "oxy derivative" and "amino derivative". Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

The term "acyl derivative", as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula R^{11e}-CO-, wherein R^{11e} is as defined above for R^{11} and may also be hydrogen. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyl, oxamoyl.

The term "amino derivative" as used herein, is defined as including -NHR^{11f} or -$NR^{11f}R^{12b}$ groups wherein R^{11f} and R^{12b} are as defined above for R^{11} and R^{12}. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl- and arylamino or mixed amino.

The term "sulfonyl derivative ", as used herein, is defined as including a group of the formula -SO_2-R^{11g}, wherein R^{11g} is as defined above for R^{11} except for "sulfonyl derivative". Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

The term "sulfinyl derivative ", as used herein, is defined as including a group of the formula -SO-R^{11h}, wherein R^{11h} is as defined above for R^{11} except for "sulfinyl derivative". Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

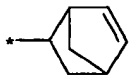
The term "heterocycle", as used herein, is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. In heterocycles comprising a S atom, the S atom may be replaced by a sulfoxide or a sulfone. Non-limiting examples of aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2,4-thiadiazolyl,

thieno(2,3-b)furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, 1,1-dioxido-1,3-thiazolidin-4-yl, sugar moieties (i.e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) or the same which can optionally be substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, or other groups as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cycloalkyl ring, a cycloalkenyl ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2.1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

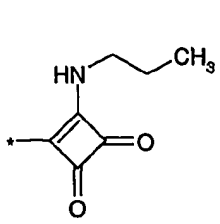
The term "heterocycle-alkyl", as used herein, represents a group of the formula -R^{14}-heterocycle in which R^{14} is C1-12- straight, branched or cyclic alkylene, or C2-12- straight or branched alkenylene or alkynylene groups. Non-limiting examples are thiophenemethyl, thiophenethyl, pyridylmethyl and pyridylethyl.

The asterisk (*) indicates the point of attachment of the substituents.

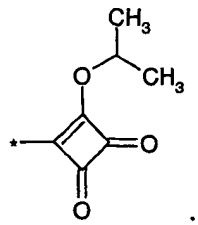
Usually, R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or an oxy derivative, or a group of formula:



Usually, R^2 is $-NR^4R^5$, $-OR^4$ or $-C(=O)NR^5R^6$; R^4 is H, $-G^1-R^8$, or a group of formula:



or



;

R^8 is aryl, heterocycle, cycloalkyl, aralkyl or -NH-aryl; and G^1 is CO, CH_2, SO_2; R^5 is H, C1-4-alkyl; or $-NR^4R^5$ represents an heterocycle or $-N=CR^9R^{10}$; R^9 is aryl and R^{10} is ether; R^6 is aryl, heterocycle, cycloalkyl or aralkyl.

Usually, R^3 is tetrazole, -CN, $-CH_2OH$ or $-CO-R^7$; and R^7 is hydroxy, amino, hydroxylamine, an oxy derivative or an amino derivative.

Preferably R^1 is cycloalkyl, aryl, aromatic heterocycle or aralkyl.

Preferably R^2 is $-NR^4R^5$, wherein R^4 and R^5 are as defined above.

Preferably R^3 is $-CO-R^7$, wherein R^7 is as defined above.

Preferably R^4 is $-G^1-R^8$, wherein G^1 and R^8 are as defined above.

Preferably R^7 is hydroxy, amino, hydroxylamino or an oxy derivative.

Preferably G^1 is CO.

Preferably R^8 is aryl, heterocycle, cycloalkyl or -NH-aryl.

Especially preferred R^1 is 2,6-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dimethoxyphenyl, 2-nitrophenyl, 2-(trifluoromethyl)phenyl, 2-bromophenyl, 2-(1,3-benzodioxol-5-yl)-1-methylethyl, 2-methoxyphenyl, 4-(methylsulfonyl)phenyl, 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl, 2,6-dimethylphenyl, 2-chloro-6-nitrophenyl, 3,5-dichloro-4-pyridinyl, 2-chloro-6-fluorophenyl, 2-methoxy-1-naphthyl, 2-mesityl.

Especially preferred R^2 is $-NHR^4$, wherein R^4 is as defined above.

Especially R^4 is $-G^1-R^8$, wherein G^1 and R^8 are as defined above.

Especially preferred R^7 is hydroxy, amino or C1-4-alkyloxy.

Especially preferred R^8 is 2,6-dichlorophenyl, 1-carboxy-1,2,2-trimethyl-3-cyclopentyl, 1-((4-methylphenyl)sulfonyl)-2-piperidinyl, 1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl, 1-(4-chlorophenyl)cyclopentyl, 2-chloro-4-(methylsulfonyl)phenyl, 2-chloro-6-methylphenyl, 3-acetyl-1,3-thiazolidin-4-yl, 2,6-dimethoxyphenyl, 2,6-dimethylphenyl, 2,6-difluorophenyl, 2-chloro-4-(methylsulfonyl)phenyl, 1-(methylsulfonyl)-2-piperidinyl, 2-methyltetrahydro-2-furanyl, 1-acetyl-2-pyrrolidinyl, 1-(phenylsulfonyl)-2-pyrrolidinyl, 2,4-dichloro-6-methyl-3-pyridinyl, 1-benzyl-5-oxo-2-pyrrolidinyl, 3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl, 1-[2-(diethylamino)ethyl]cyclopentyl.

Best R^1 is 2,6-dichlorophenyl, 2,6-dimethoxyphenyl, 3,5-dichloro-4-pyridinyl, 2-nitrophenyl, 2-chloro-6-fluorophenyl, 2-methoxy-1-naphthyl, 2-chloro-6-nitrophenyl.

Best R^2 is $-NH-C(=O)-R^8$, wherein R^8 is as defined above.

Best R^7 is hydroxy or C1-4-alkyloxy.

Best R^8 is 2,6-dichlorophenyl, 1-carboxy-1,2,2-trimethyl-3-cyclopentyl , 1-((4-methylphenyl)sulfonyl)-2-piperidinyl, 1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl, 1-(4-chlorophenyl)cyclopentyl, 2-chloro-4-(methylsulfonyl)phenyl, 2-chloro-6-methylphenyl, 1-(phenylsulfonyl)-2-pyrrolidinyl, 2,4-dichloro-6-methyl-3-pyridinyl, 1-benzyl-5-oxo-2-pyrrolidinyl.

Combinations of one or more of these preferred compound groups are especially preferred.

More preferred compounds are: methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethylbenzoyl)amino]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(4-pyridinyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-difluorobenzoyl)amino]propanoic acid; methyl (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-({[[2,6-dichlorophenyl)amino]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; (1R,3S)-3-[({1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-difluorobenzoyl)amino]propanoic acid; (2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-

[(2,6-dichlorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-nitrophenyl]-6-quinolinyl}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; 2,6-dichloro-N-[1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-(hydroxyamino)-2-oxoethyl]benzamide; N-(2-amino-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide; methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoate; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoic acid; {[2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoyl}oxy)methyl pivalate; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-chlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2-bromophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 3-[2-(2-bromophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-bromophenyl)-6-quinolinyl]propanoic acid; 3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}-2-[(2,6-

dichlorobenzoyl)amino]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}-2-{{{(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; 2-[{{(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-cyclohexyl-6-quinolinyl)propanoic acid; 3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid; 3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,3-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,3-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid; 3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 3-[2-(2,4-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-[(2,6-difluorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-mesityl-6-quinolinyl)propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-(2-mesityl-6-quinolinyl)propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic

acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,3-difluorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; (-)-methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate; (-)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; (+)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({{[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid; methyl 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate; methyl (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; (1R,3S)-3-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1,2,2-trimethylcyclopentanecarboxylic acid; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; (1R,3S)-3-[({(1S)-1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-({[(4R)-3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoate; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; 2-{[(1-

aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({1-[2-(diethylamino)ethyl]cyclopentyl}carbonyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate; methyl (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid and 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid, and pharmaceutically acceptable salts thereof.

Most preferred compounds are: methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethylbenzoyl)amino]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; methyl (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; (1R,3S)-3-[({1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-

nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-nitrophenyl]-6-quinolinyl}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; N-(2-amino-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoic acid; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-bromophenyl)-6-quinolinyl]propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; 3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-[(2,6-difluorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-mesityl-6-quinolinyl)propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-(2-mesityl-6-quinolinyl)propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-

{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid; 3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; (-)-methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate; (-)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid; methyl 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate; methyl (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; (1R,3S)-3-[({(1S)-1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-{{[(4R)-3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl]carbonyl}amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({1-[2-(diethylamino)ethyl]cyclopentyl}carbonyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate; methyl (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid and 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-

(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid, and pharmaceutically acceptable salts thereof.

Best compounds are: methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; methyl (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; (1R,3S)-3-[({1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-nitrophenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; 2-[(((2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; (-)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid; methyl (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate;

methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; (1R,3S)-3-[({(1S)-1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid and 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid and pharmaceutically acceptable salts thereof.

The best results have been obtained with the following compounds: (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid and (-)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid.

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30.

In all the above-mentioned scopes, when the carbon atom to which R^2 and R^3 are attached is asymmetric, it is preferably in the "S"-configuration.

The "pharmaceutically acceptable salts" according to the invention include therapeutically active, non-toxic base and acid salt forms which the compounds of formula I are able to form.

The acid addition salt form of a compound of formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like (Handbook of Pharmaceutical

Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta - Zürich, 2002, 329-345).

The compounds of formula I containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like (Hanbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta - Zürich, 2002, 329-345).

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

Furthermore certain compounds of formula I which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the invention includes both mixture and separate individual isomers.

Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitely indicated in the above formula, such forms are intended to be included within the scope of the present invention.

The invention also includes within its scope pro-drug forms of the compounds of formula I and its various sub-scopes and sub-groups.

The term "prodrug" as used herein includes compound forms, which are rapidly transformed *in vivo* to the parent compound according to the invention, for example, by

hydrolysis in blood. Prodrugs are compounds bearing groups that are removed by biotransformation prior to exhibiting their pharmacological action. Such groups include moieties that are readily cleaved in vivo from the compound bearing it, which compound after cleavage remains or becomes pharmacologically active. Metabolically cleavable groups form a class of groups well known to practitioners of the art. They include, but are not limited to such groups as alkanoyl (i.e. acetyl, propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aroyl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate, sulfonyl, sulfinyl and the like. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group (T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A.C.S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987).

The protecting group P may be any suitable amine protecting group such as, for example, esters, sulfenyl derivatives, sulfonyl derivatives, alkyl and aryl. Non-limiting examples are methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (Fmoc), 9-(2-sulfo)fluorenylmethoxycarbonyl, 9-(2,7-dibromo)fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl (Troc), 2-phenylethoxycarbonyl, 2-chloroethoxycarbonyl, benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, benzenesulfenyl, 2-nitrobenzenesulfenyl, tosyl, benzenesulfonyl, methyl, tert-butyl, allyl, benzyl, bis(4-methoxyphenyl)methyl or 2,4-dinitrophenyl. For more details concerning deprotection methods, see "Protective Groups in Organic Chemistry", Chapter 2, J.F.W. Omie, Plenum Press, London and New York, 1973 and "Protective Groups in Organic Synthesis", Chapter 7, Th. W. Greene, John Wiley & Sons, 1999.

The present invention concerns also processes for preparing the compounds of formula I.

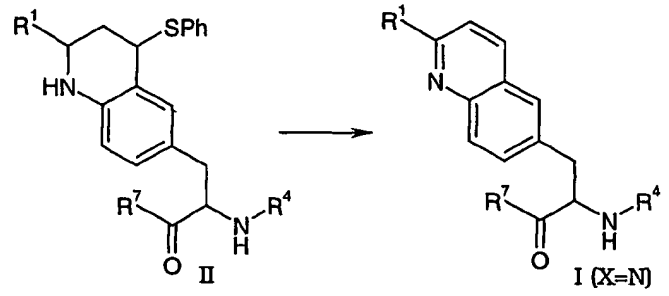
The compounds of formula I according to their invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry.

The following process description sets forth certain synthesis routes in an illustrative manner. Other alternative and/or analogous methods will be readily apparent

to those skilled in this art. As used herein in connection with substituent meanings, "=" means "is" and "≠" means "is other than".

Compounds of formula I may be prepared according to one of the following procedures.

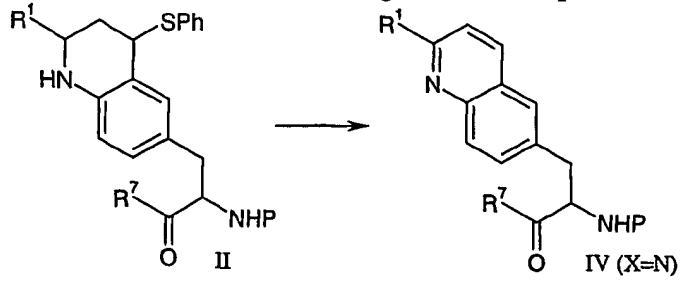
Compounds of formula I wherein X = N, R^1 ≠ oxy derivative, R^2 = -NHR^4, wherein R^4 has the same definition as described above for compounds of general formula I, and R^3 = -COR^7, with R^7 = OH or an oxy derivative, may be prepared by oxidation and aromatisation of a derivative of formula II according to the equation:



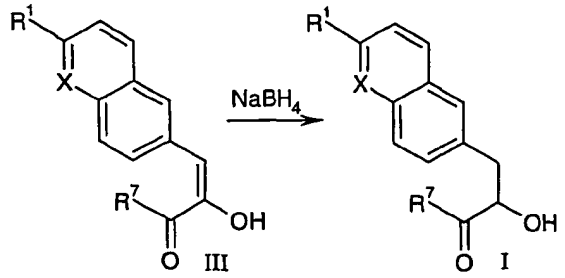
wherein R^1, R^2 and R^4 have the same definitions as described above and Ph represents a phenyl group.

Oxidation may be carried out with $NaIO_4$ in dioxane/H_2O or in a mixture alcohol/H_2O, with H_2O_2 in methanol, with tert-butyl hydroperoxide (TBHP) in toluene or alcohol or with meta-chloro-perbenzoic acid (mCPBA) in an inert solvent such as dichloromethane. The following elimination is carried out in a mixture dioxane/H_2O, at a temperature between 40 and 80 °C.

Compounds of formula IV wherein X = N, R^1 ≠ oxy derivative, R^2 = -NHR^4, wherein R^4 is P, P being a protecting group, and R^3 = -COR^7, with R^7 = OH or an oxy derivative, may be prepared according to the same procedure:

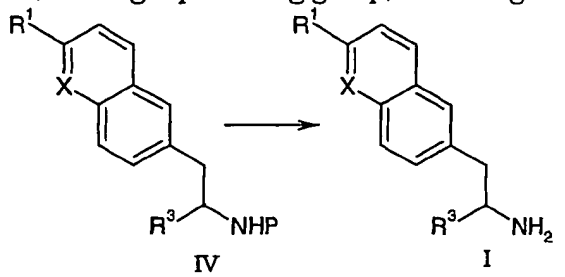


Compounds of formula I wherein R^2 = OH and R^3 = -COR^7, with R^7 = OH or an oxy derivative, may be prepared by reduction of a compound of formula III according to equation:



This reaction may be carried out according to any procedure known to the person skilled in the art.

Compounds of formula I wherein R^2 = -NH_2 and R^3 = -COR^7, R^7 being hydroxy or an oxy derivative, may be obtained by deprotection of compounds of formula IV wherein R^2 = NHP, P being a protecting group, according to the equation:



This transformation may be carried out according to any procedure known to the person skilled in the art.

Compounds of formula I wherein R^3 = -COOH may be prepared by hydrolysis of the corresponding compound of formula I wherein R^3 = -COR^7, R^7 being amino, an oxy derivative or an amino derivative.

This transformation may be carried out according to any procedure known to the person skilled in the art.

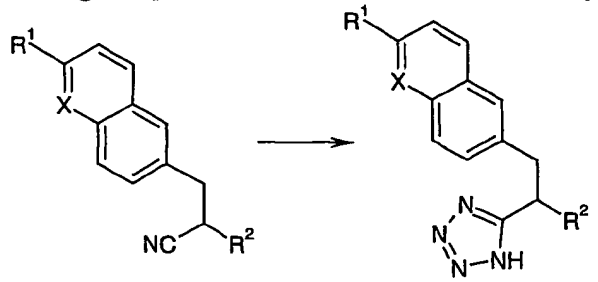
Compounds of formula I wherein R^3 = -COR^7 with R^7 = amino derivative may be prepared by reaction of the corresponding compound of formula I wherein R^3 = -COOH with an amine:

This transformation may be carried out according to any procedure known to the person skilled in the art, or according to the procedure described in S. Conti, Tetrahedron (1994), 50 (47), 13493-13500.

Compounds of formula I wherein R^3 = -CN may be prepared from the corresponding compound of formula I wherein R^3 = $-CONH_2$.

This reaction may be carried out according to the procedure described in S. Conti, Tetrahedron (1994), 50 (47), 13493-13500.

Compounds of formula I wherein R^3 = tetrazole may be prepared from the corresponding compound of formula I wherein R^3 = cyano according to the equation:



I with R^3 = CN I with R^3 = tetrazole

This reaction may be carried out according to the procedure described in J.G. Buchanan, J. Chem. Soc., Perkin Trans. 1 (1992), 20, 2593-2601.

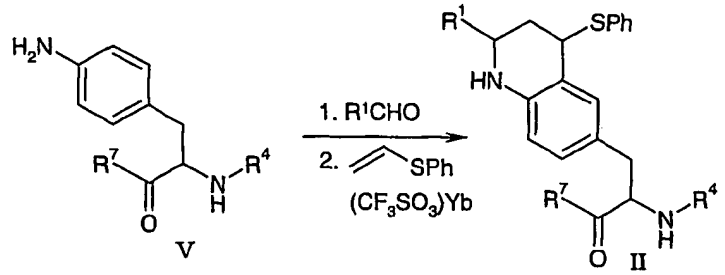
Compounds of formula I wherein R^3 = $-CH_2OH$ may be prepared by reduction of the corresponding compound of formula I wherein R^3 = $-COR^7$, R^7 being an oxy derivative. This transformation may be carried out according to any procedure known to the person skilled in the art.

Compounds of formula I wherein R^2 = $-NR^4R^5$, R^5 being a C1-4 alkyl, and R^3 = $-COR^7$, R^7 being an oxy derivative, may be prepared by alkylation of the corresponding compound of formula I wherein R^5 = H. This transformation may be carried out according to any procedure known to the person skilled in the art.

Compounds of formula I wherein R^2 = $-NHR^4$ and R^3 = $-COR^7$, R^7 being an oxy derivative, may be prepared by acylation, sulfonylation or alkylation of the corresponding compound of formula I wherein R^2 = NH_2. This transformation may be carried out according to any procedure known to the person skilled in the art.

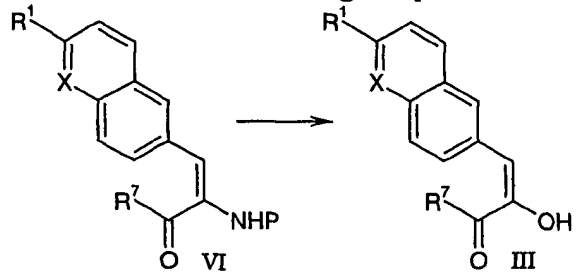
Compounds of formula I wherein R^2 = -OR^4 and R^3 = -COR^7, R^7 being an oxy derivative, may be prepared by alkylation or acylation of the corresponding compound of formula I wherein R^2 = OH. This transformation may be carried out according to any procedure known to the person skilled in the art.

Compounds of formula II may be prepared by reaction of a compound of formula V with an aldehyde, phenyl vinyl sulfide and an ytterbium triflate derivative according to equation:



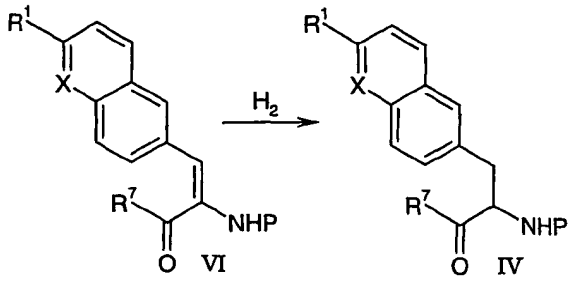
This reaction may be carried out according to the procedure described in S. Kobayashi et al., Synthesis (1995), 1195-1202.

Compounds of formula III may be prepared by deprotection and hydrolysis of a compound of formula VI according to equation:



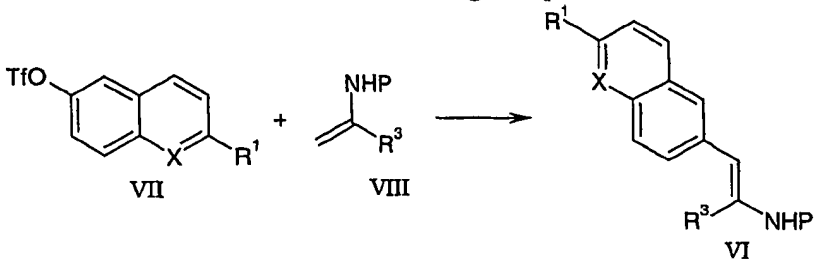
This deprotection followed by hydrolysis of the resulting enamine may be carried out according to procedure described in "Protective Groups in Organic Synthesis", Chapter 4, Th. W. Greene, John Wiley & Sons, 1999.

Compounds of formula IV may be prepared by hydrogenation of a compound of formula VI according to equation:



This reaction may be carried out according to the procedure described in M.A. Vela et al., J. Org. Chem. (1990), 55, 2913-2918.

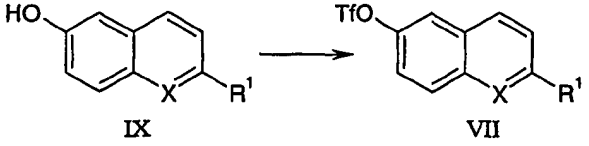
Compounds of formula VI may be prepared by reaction of a compound of formula VII with a derivative of formula VIII according to equation:



This reaction may be carried out according to the procedure described in A. Arcadi et al, Tetrahedron (1990), 46 (20), 7151-7164.

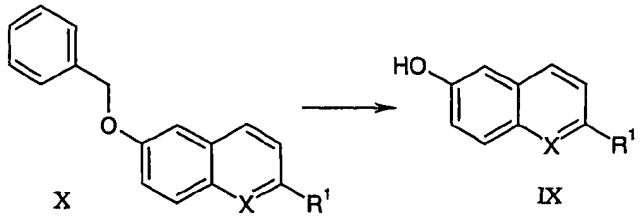
Compounds of formula VIII are commercially available or, when R^3 = -COR^7, may be prepared by dehydration of 2-amino-protected 3-hydroxypropanoate ester derivatives, for example according to the procedure described in K. Goodall et al., J. Chem. Res. Synop. (2000), 2, 54-55.

Compounds of formula VII may be prepared by modification of a compound of formula IX according to equation:



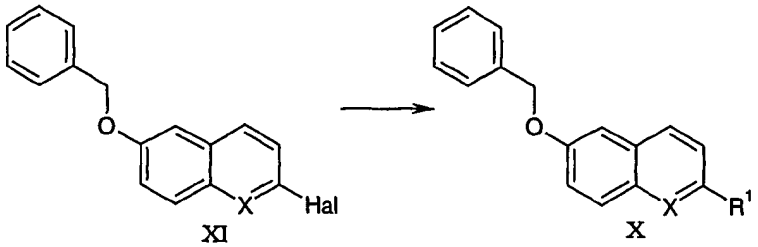
This reaction may be carried out for example according to the procedures described in H. Kosuki et al., Synthesis (1990), 12, 1145-1147; K. Koch, J. Org. Chem. 1994, 59, 1216-1218 or V. Drachsler et al., Synlett (1998), 11, 1207-1208.

For the synthesis of derivatives of formula IX, a derivative of formula X may be deprotected either by catalytic hydrogenation (when R^1 = oxy derivative) or by treatment with BBr_3 (when $R^1 \neq$ oxy derivative) according to equation:



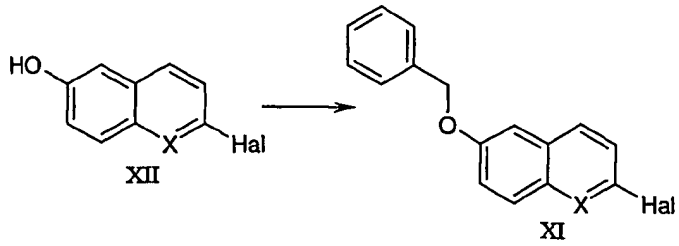
This reaction may be carried out according to procedures described in "Protective Groups in Organic Synthesis", Th. W. Greene, John Wiley & Sons, 1999.

For the synthesis of derivatives of formula X, a derivative of formula XI wherein Hal = Cl or Br is modified either with boronic derivatives ($R^1 \neq$ oxy derivative) or by reaction with alcohol (R^1 = oxy derivative) according to equation:



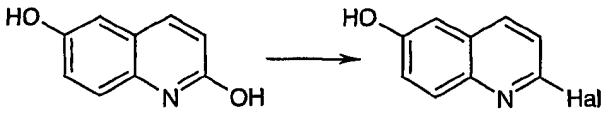
This reaction may be carried out according to the procedure described in N.M. Ali et al., Tetrahedron (1992), 48, 8117-8126.

For the synthesis of derivatives of formula XI, the hydroxy group of a derivative of formula XII is protected according to equation:



This reaction may be carried out according to procedures described in "Protective Groups in Organic Synthesis", Chapter 2, Th. W. Greene, John Wiley & Sons, 1999.

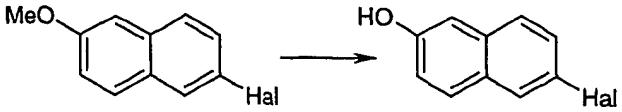
For the synthesis of derivatives of formula XII wherein X = N, a derivative of formula XIII reacts with $PO(Hal)_3$, for example $POCl_3$ or $POBr_3$, according to equation:



XIII XII (X = N)

This reaction may be carried out according to the procedure described in Y. Tagawa et al., Heterocycles (1998), 48, 2379-2387 or in M. Fernandez et al., Heterocycles (1994), 38, 2615-2620.

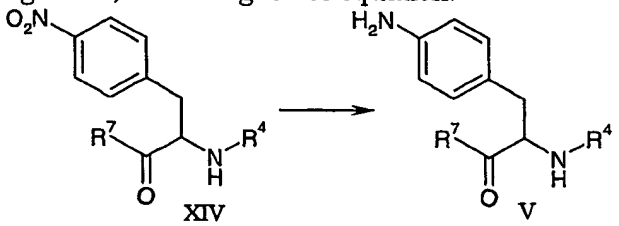
For the synthesis of derivatives of formula XII wherein X = CH, a derivative of formula XIIIa may be deprotected, for example by treatment with BBr_3, according to equation:



XIIIa XII (X = CH)

This reaction may be carried out according to procedures described in "Protective Groups in Organic Synthesis", Chapter 2, Th. W. Greene, John Wiley & Sons, 1999.

Compounds of formula V may be prepared by reduction of a compound of formula XIV either by catalytic hydrogenation ($R^7 \neq$ O-Wang Resin) or by treatment with $SnCl_2$ (R^7 = O-Wang Resin) according to the equation:

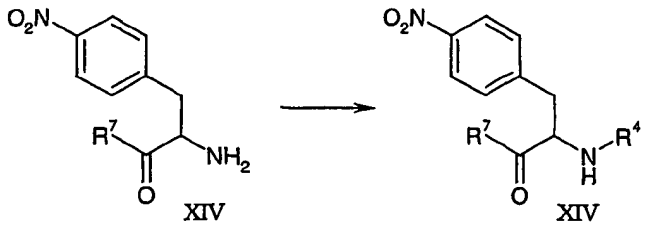


XIV V

This reaction may be carried out according to any procedure known to the person skilled in the art or to the procedure described in PCT patent application WO9834115-A1 for compounds attached to the Wang Resin.

Compounds of formula XIV may be prepared according to one of the following procedures:

When in formula XIV, R^7 = oxy derivative, the corresponding compound of formula XIV wherein R^4 = H is alkylated, acylated or sulfonylated according to equation:



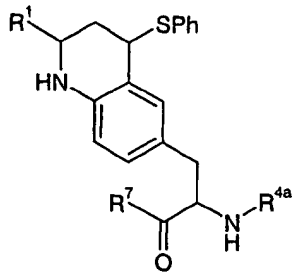
This transformation may be carried out according to any procedure known to the person skilled in the art.

When in formula XIV, $R^2 = NH_2$ and $R^3 = -COR^7$, with R^7 = oxy derivative, the corresponding compound of formula XIV wherein R^7 = hydroxy is esterified. This transformation may be carried out according to any procedure known to the person skilled in the art.

Compound of formula XIV wherein $R^2 = NH_2$ and $R^3 = -COR^7$, with R^7 = O-Wang Resin may be obtained by deprotection of the corresponding compound of formula XIV wherein R^2 = NHP, P being a protecting group, and R^7 = O-Wang Resin. This transformation may be carried out according to any procedure known to the person skilled in the art.

When compounds of formula I present one or several stereogenic centres, and that non-stereoselective methods of synthesis are used, resolution of the mixture of stereoisomers can best be effected in one or several steps, involving generally sequential separation of mixtures of diastereomers into their constituting racemates, using preferably chromatographic separations on achiral or chiral phase in reversed or preferably in direct mode, followed by at least one ultimate step of resolution of each racemate into its enantiomers, using most preferably chromatographic separation on chiral phase in reversed or preferably in direct mode. Alternatively, when partly stereoselective methods of synthesis are used, the ultimate step may be a separation of diastereomers using preferably chromatographic separations on achiral or chiral phase in reversed or preferably in direct mode.

In another embodiment, the present invention concerns also the synthesis intermediates of formula II

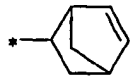


II

wherein

R^{4a} is R^4 or P, R^4 being as defined above for compounds of formula I,

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or a group of formula:



,

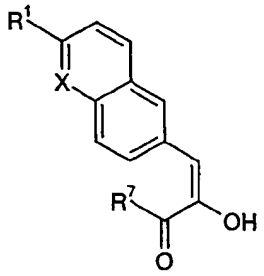
R^7 is hydroxy or an oxy derivative,

and P is an amine protecting group.

Preferably, the synthesis intermediates of formula II are selected from the group consisting of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-(benzoylamino)-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[4-(phenylsulfanyl)-2-(1,3-thiazol-2-yl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[4-(phenylsulfanyl)-2-(4-pyridinyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl

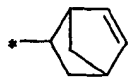
(2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethylphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate and methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate.

In another embodiment, the present invention concerns also the synthesis intermediates of formula III



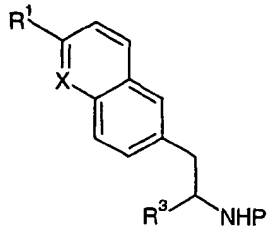
III

wherein X and R^1 are as defined above for compounds of formula I and R^7 is hydroxy or an oxy derivative, with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:



Preferably, the synthesis intermediate of formula III is methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxy-2-propenoate.

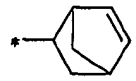
In another embodiment, the present invention concerns also the synthesis intermediates of formula IV



IV

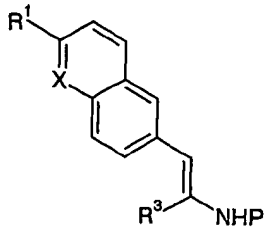
wherein X and R^1 are as defined above for compounds of formula I,
R^3 is -CO-R^7,

R^7 is hydroxy or an oxy derivative,
and P is an amine protecting group,
with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:



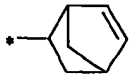
Preferably, the synthesis intermediates of formula IV are selected from the group consisting of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenyl-6-quinolinyl)propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl)propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(4-chlorophenoxy)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-methoxy-6-quinolinyl)propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; methyl 2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate and ethyl 2-(acetylamino)-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoate.

In another embodiment, the present invention concerns also the synthesis intermediates of formula VI



VI

wherein X and R^1 are as defined above for compounds of formula I,
R^3 is -CO-R^7,
R^7 is hydroxy or an oxy derivative,
and P is an amine protecting group,
with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:



Preferably, the synthesis intermediates of formula VI are selected from the group consisting of methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl)-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(4-chlorophenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-methoxy-6-quinolinyl)-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-propenoate and methyl (2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-propenoate.

In another embodiment, the present invention concerns also the synthesis intermediates selected from the group consisting of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(4-nitrophenyl)propanoate; methyl 2-[(2,6-dichlorobenzyl)amino]-3-(4-nitrophenyl)propanoate; methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzoyl)amino]propanoate; methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzyl)amino]propanoate; 6-(benzyloxy)-2-chloroquinoline; 6-(benzyloxy)-2-phenoxyquinoline; 6-(benzyloxy)-2-(4-chlorophenoxy)quinoline; 6-(benzyloxy)-2-methoxyquinoline; 6-(benzyloxy)-2-(2-methoxyphenoxy)quinoline; 6-(benzyloxy)-2-(2,6-dimethoxyphenoxy)quinoline; 6-(benzyloxy)-2-(2,6-dichlorophenoxy)quinoline; 2-phenoxy-6-quinolinol; 2-(4-chlorophenoxy)-6-quinolinol; 2-methoxy-6-quinolinol; 2-(2-methoxyphenoxy)-6-quinolinol; 2-(2,6-dimethoxyphenoxy)-6-quinolinol; 2-(2,6-dichlorophenoxy)-6-quinolinol; 2-phenoxy-6-quinolinyl trifluoromethanesulfonate; 2-(4-chlorophenoxy)-6-quinolinyl trifluoromethanesulfonate; 2-methoxy-6-quinolinyl trifluoromethanesulfonate; 2-(2-methoxyphenoxy)-6-quinolinyl trifluoromethanesulfonate;

2-(2,6-dimethoxyphenoxy)-6-quinolinyl trifluoromethanesulfonate; 2-(2,6-dichlorophenoxy)-6-quinolinyl trifluoromethanesulfonate; 6-(benzyloxy)-2-(2,6-dichlorophenyl)quinoline; 2-(2,6-dichlorophenyl)-6-quinolinol; 2-(2,6-dichlorophenyl)-6-quinolinyl trifluoromethanesulfonate; 2-(benzyloxy)-6-(2,6-dimethoxyphenyl)naphthalene; 6-(2,6-dimethoxyphenyl)-2-naphthol and 6-(2,6-dimethoxyphenyl)-2-naphthyl trifluoromethanesulfonate.

It has now been found that compounds of formula I and their pharmaceutically acceptable salts are useful in a variety of pharmaceutical indications.

For example, the compounds according to the invention are useful for the treatment of asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis.

Thus, the present invention, in a further aspect, concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders such as mentioned above.

In particular, the present invention concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of VLA-4 dependent inflammatory diseases such as for example asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis.

The compounds of the invention are useful for treating conditions in which there is an influx of leukocytes in the tissues. These conditions include preferably asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis. The compounds exhibit this biological activity by inhibiting the VCAM/VLA-4 interaction.

Subjects in need of treatment for a VLA-4 dependent inflammatory condition, preferably asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis,

multiple sclerosis and other autoimmune disorders, and atherosclerosis, can be treated by administering to the patient an effective amount of one or more of the above-identified compounds or a pharmaceutically acceptable derivative or salt thereof in a pharmaceutically acceptable carrier or diluent to reduce formation of oxygen radicals. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, intramuscularly or topically, in liquid, cream, gel or solid form, via a buccal or nasal spray, or aerosol.

The invention further concerns the use of the compounds of formula I for the manufacture of a medicament for therapeutic application. In particular, the invention concerns the use of the compounds of formula I for the manufacture of a medicament useful for treating conditions in which there is likely to be a VLA-4 dependent inflammatory component. The invention concerns the use of the compound of formula I for the manufacture of a medicament useful for treating asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis.

The invention further concerns the compounds of formula I for use as medicaments. The invention concerns the compounds of formula I for use as a medicament for treating asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis.

The activity and properties of the active compounds, oral availability and stability in vitro or in vivo can vary significantly among the optical isomers of the disclosed compounds.

In a preferred embodiment, the active compound is administered in an enantiomerically enriched form, i.e., substantially in the form of one isomer.

The present invention also concerns a method for treating VLA-4 dependent inflammatory condition (preferably asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis) in a mammal in need of such treatment, comprising administering a therapeutic dose of at least one compound of formula I or a pharmaceutically acceptable

salt thereof to a patient.

The methods of the invention comprise administration to a mammal (preferably human) suffering from above mentioned conditions or disorders, of a compound according to the invention in an amount sufficient to alleviate or prevent the disorder or condition.

The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 0.01 to 1000 mg, preferably 0.05 to 500 mg of active ingredient per unit dosage form.

The term "treatment" as used herein includes curative treatment and prophylactic treatment.

By "curative" is meant efficacy in treating a current symptomatic episode of a disorder or condition.

By "prophylactic" is meant prevention of the occurrence or recurrence of a disorder or condition.

The activity of the compounds of formula I, or their pharmaceutically acceptable salts, as VLA-4 antagonists can be determined in a cell adhesion assay. The objective of this test is to evaluate the anti-VLA-4 potential of a compound by measuring its inhibitory effect on the adhesion of a VLA-4 expressing cell line to human recombinant VCAM (adapted from A. L. Akeson et al., J. Immunol. Methods (1993), 163, 181-185).

Results obtained with compounds of formula I are indicative of a strong pharmacological effect.

For treating diseases, compounds of formula I or their pharmaceutically acceptable salts, may be employed at an effective daily dosage and administered in the form of a pharmaceutical composition.

Therefore, another embodiment of the present invention concerns a pharmaceutical composition comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable diluent or carrier.

To prepare a pharmaceutical composition according to the invention, one or more of the compounds of formula I or a pharmaceutically acceptable salt thereof, is intimately admixed with a pharmaceutical diluent or carrier according to conventional pharmaceutical compounding techniques known to the skilled practitioner.

Suitable diluents and carriers may take a wide variety of forms depending on the desired route of administration, e.g., oral, rectal, or parenteral.

Pharmaceutical compositions comprising compounds according to the invention can, for example, be administered orally or parenterally, i.e., intravenously.

intramuscularly, subcutaneously or intrathecally.

Pharmaceutical compositions suitable for oral administration can be solids or liquids and can, for example, be in the form of tablets, pills, dragees, gelatine capsules, solutions, syrups, and the like.

To this end the active ingredient may be mixed with an inert diluent or a non-toxic pharmaceutically acceptable carrier such as starch or lactose. Optionally, these pharmaceutical compositions can also contain a binder such as microcrystalline cellulose, gum tragacanth or gelatine, a disintegrant such as alginic acid, a lubricant such as magnesium stearate, a glidant such as colloidal silicon dioxide, a sweetener such as sucrose or saccharin, or colouring agents or a flavouring agent such as peppermint or methyl salicylate.

The invention also contemplates compositions which can release the active substance in a controlled manner. Pharmaceutical compositions which can be used for parenteral administration are in conventional form such as aqueous or oily solutions or suspensions generally contained in ampoules, disposable syringes, glass or plastics vials or infusion containers.

In addition to the active ingredient, these solutions or suspensions can optionally also contain a sterile diluent such as water for injection, a physiological saline solution, oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, antibacterial agents such as benzyl alcohol, antioxidants such as ascorbic acid or sodium bisulphite, chelating agents such as ethylene diamine-tetra-acetic acid, buffers such as acetates, citrates or phosphates and agents for adjusting the osmolarity, such as sodium chloride or dextrose.

These pharmaceutical forms are prepared using methods which are routinely used by pharmacists.

The amount of active ingredient in the pharmaceutical compositions can fall within a wide range of concentrations and depends on a variety of factors such as the patient's sex, age, weight and medical condition, as well as on the method of administration. Thus the quantity of compound of formula I in compositions for oral administration is at least 0.5 % by weight and can be up to 80 % by weight with respect to the total weight of the composition.

For the preferred oral compositions, the daily dosage is in the range 0.01 to 1000 milligrams (mg) of compounds of formula I.

In compositions for parenteral administration, the quantity of compound of formula I present is at least 0.5 % by weight and can be up to 33 % by weight with

respect to the total weight of the composition. For the preferred parenteral compositions, the dosage unit is in the range 0.01 mg to 1000 mg of compounds of formula I.

The daily dose can fall within a wide range of dosage units of compound of formula I and is generally in the range 0.01 to 1000 mg. However, it should be understood that the specific doses could be adapted to particular cases depending on the individual requirements, at the physician's discretion.

The following examples are provided for illustrative purposes only and are not intended, nor should they be construed, as limiting the invention in any manner. Those skilled in the art will appreciate that routine variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

Unless specified otherwise in the examples, characterization of the compounds is performed according to the following methods:

NMR spectra are recorded on a BRUKER AC 250 Fourier Transform NMR Spectrometer fitted with an Aspect 3000 computer and a 5mm $^{1}H/^{13}C$ dual probehead or BRUKER DRX 400 FT NMR fitted with a SG Indigo^{2} computer and a 5 mm inverse geometry $^{1}H/^{13}C/^{15}N$ triple probehead. The compound is studied in DMSO-d_6 (or $CDCl_3$) solution at a probe temperature of 313 K or 300 K and at a concentration of 20 mg/ml. The instrument is locked on the deuterium signal of DMSO-d_6 (or $CDCl_3$). Chemical shifts are given in ppm downfield from TMS taken as internal standard.

HPLC analyses are performed using one of the following systems:

- an Agilent 1100 series HPLC system mounted with an INERTSIL ODS 3 C18, DP 5 µm, 250 X 4.6 mm column. The gradient ran from 100 % solvent A (acetonitrile, water, H_3PO_4 (5/95/0.001, v/v/v)) to 100 % solvent B (acetonitrile, water, H_3PO_4 (95/5/0.001, v/v/v)) in 6 min with a hold at 100 % B of 4 min. The flow rate is set at 2.5 ml/min. The chromatography is carried out at 35°C.

- a HP 1090 series HPLC system mounted with a HPLC Waters Symetry C18, 250 X 4.6 mm column. The gradient ran from 100 % solvent A (MeOH, water, H_3PO_4 (15/85/0.001M, v/v/M)) to 100 % solvent B (MeOH, water, H_3PO_4 (85/15/0.001 M, v/v/M)) in 10 min with a hold at 100 % B of 10 min. The flow rate is set at 1 ml/min. The chromatography is carried out at 40 °C.

Mass spectrometric measurements in LC/MS mode are performed as follows:

HPLC conditions

Analyses are performed using a WATERS Alliance HPLC system mounted with an INERTSIL ODS 3, DP 5 µm, 250 X 4.6 mm column.

The gradient ran from 100 % solvent A (acetonitrile, water, TFA (10/90/0.1, v/v/v)) to 100 % solvent B (acetonitrile, water, TFA (90/10/0.1, v/v/v)) in 7 min with a hold at 100 % B of 4 min. The flow rate is set at 2.5 ml/min and a split of 1/25 is used just before API source.

MS conditions

Samples are dissolved in acetonitrile/water, 70/30, v/v at the concentration of about 250 μgr/ml. API spectra (+ or -) are performed using a FINNIGAN (San Jose, CA, USA) LCQ ion trap mass spectrometer. APCI source operated at 450 °C and the capillary heater at 160 °C. ESI source operated at 3.5 kV and the capillary heater at 210 °C.

Mass spectrometric measurements in DIP/EI mode are performed as follows: samples are vaporized by heating the probe from 50 °C to 250 °C in 5 min. EI (Electron Impact) spectra are recorded using a FINNIGAN (San Jose, CA, USA) TSQ 700 tandem quadrupole mass spectrometer. The source temperature is set at 150 °C.

Specific rotation is recorded on a Perkin-Elmer 341 polarimeter. The angle of rotation is recorded at 25 °C on 1 % solutions in MeOH. For some molecules, the solvent is CH_2Cl_2 or DMSO, due to solubility problems.

Preparative chromatographic separations are performed on silicagel 60 Merck, particle size 15-40 μm, reference 1.15111.9025, using Novasep axial compression columns (80 mm i.d.), flow rates between 70 and 150 ml/min. Amount of silicagel and solvent mixtures as described in individual procedures.

Preparative Chiral Chromatographic separations are performed on a DAICEL Chiralpak AD 20 μm, 100*500 mm column using an in-house build instrument with various mixtures of lower alcohols and C5 to C8 linear, branched or cyclic alkanes at ± 350 ml/min. Solvent mixtures as described in individual procedures.

The following abbreviations are used in the examples:

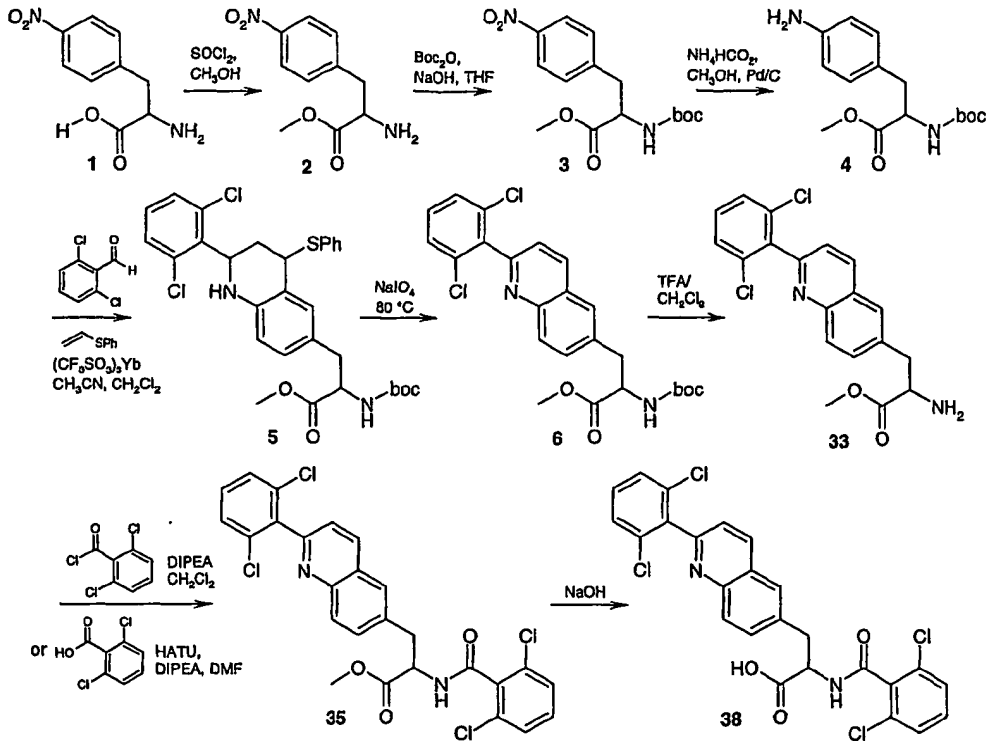
aa	Amino acid
Ac	$-C(=O)CH_3$
AcOEt	Ethyl acetate
AcOH	Acetic acid
Boc	tert-butoxycarbonyl
CH_3CN	Acetonitrile
ClCOOEt or $ClCO_2Et$	Ethyl chloroformate
DIPEA	Diisopropylethylamine

DMF	N,N-Dimethylformamide
Equ.	Equivalent
Et_3N	Triethylamine
HATU	O-7-azabenzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluoro-phosphate
HOBT	1-hydroxybenzotriazole
mCPBA	meta-chloro-perbenzoic acid
PrepLC	Preparative Liquid Chromatography
RT	Room temperature
TBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
Tf-	Trifluoromethylsulfonyl group
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Example 1. Quinolinyl derivatives: racemic synthesis.

1.1 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **38**.

Scheme 1:



1.1.1 Synthesis of methyl 2-amino-3-(4-nitrophenyl)propanoate **2**:

To a suspension of 4-nitrophenylalanine **1** (25 g) in methanol (10 ml/g) at 0 °C is added $SOCl_2$ (2 equ.). After 30 minutes, the reaction is stirred at room temperature for 1 night. Volatiles are then evaporated and the residue is diluted in water. The solution is alkalinized with NaOH 2N and extracted with CH_2Cl_2. The organic phase is dried over $MgSO_4$ and evaporated. No further purification is needed.

Yield : 79 %.

MS (MH^+): 225.

1.1.2 Synthesis of methyl 2-[(tert-butoxycarbonyl)amino]-3-(4-nitrophenyl)propanoate **3**:

Methyl 2-amino-3-(4-nitrophenyl)propanoate **2** (21 g) and powdered NaOH (1.2 equ.) are suspended in THF (5 ml/g). Boc_2O (1.2 equ.) solubilized in THF (2 ml/g) is added slowly to the solution. The mixture is stirred for 1 h at room temperature, poured into water and then extracted with AcOEt (2 x 900 ml). The organic phase is dried over $MgSO_4$ and evaporated to dryness. No further purification is needed.

Yield: 100 %.

MS (MH^+): 325.

1.1.3 Synthesis of methyl 3-(4-aminophenyl)-2-[(tert-butoxycarbonyl)amino]propanoate **4**:

To a solution of methyl 2-[(tert-butoxycarbonyl)amino]-3-(4-nitrophenyl)propanoate **3** (69.4 g) and NH_4HCO_2 (6.5 equ.) in CH_3OH (20 ml/g) is added 5 % Pd/C (15 % in weight, 10 g). The temperature rises to 40 °C and then decreases. After stirring for 2 h at room temperature, the solution is filtered over celite and the solvent is evaporated. The residue is diluted in AcOEt and washed 3 times with water. The organic phase is dried over $MgSO_4$ and evaporated to dryness. No further purification is needed.

Yield: 100 %.

MS (MH^+): 285.

1.1.4 Synthesis of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **5**:

Methyl 3-(4-aminophenyl)-2-[(tert-butoxycarbonyl)amino]propanoate **4** (38.2 g) solubilized in a 50/50 mixture of CH_3CN/CH_2Cl_2 is added, at room temperature, to a mixture of $Yb(OTf)_3$ (0.05equ.) and $MgSO_4$ (3equ.) in CH_3CN/CH_2Cl_2 (50/50, 400 ml). Solid 2,6-dichlorobenzaldehyde (1.1 equ.) is then added and after 2 h, phenyl vinyl sulfide (1.2 equ.) is added dropwise. After one night, insolubles are filtered and the solvents evaporated. The residue is purified by silica gel chromatography using hexane mixture/AcOEt 80/20 as eluent to give methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **5**.

Yield : 81 %.

MS (MH^+):587/589/591.

Methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **5a** and methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **5b** (MS (MH^+): 579) can be synthesized according to the same method.

1.1.5 Synthesis of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **6**:

Methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **5** (32 g) is solubilized in dioxane (10 ml/g of **5**). Water (0.5 ml/g of **5**) and solid $NaIO_4$ (1.1 equ.) are added, and

the mixture is stirred at 80 °C for 40 h. The solvent is evaporated and the resulting mixture is extracted with CH_2Cl_2. The insoluble part is filtered and after evaporation, the residue is purified by silica gel chromatography using Hexane mixture/AcOEt 75/25 as eluent.

Yield: 88 %.

MS (MH^+): 475/477/479.

Methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenyl-6-quinolinyl)propanoate **6a** and methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate **6b** (MS (MH^+): 467) can be synthesized according to the same method.

1.1.6 Synthesis of methyl 2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **33**:

9.15 g of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **6** are solubilized in CH_2Cl_2 (50 ml). TFA (50 ml) is added at 0 °C, and the mixture is stirred at RT for 6 h. After evaporation of the solvent, the residue is triturated in diethyl ether and cooled at 5 °C. The solid product **33** is obtained by filtration.

Yield: 89 %.

MS (MH+): 375/377/379.

1.1.7 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **35**:

To 23.38 g of methyl 2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **33** (.2 TFA salt) in CH_2Cl_2 (50 ml) are added, at 0 °C, triethylamine (22 ml) and 2,6-dichlorobenzoyl chloride (6.22 ml) dissolved in CH_2Cl_2 (6 ml). The reaction is stirred at RT for 2 h. The organic phase is washed with water, dried over $MgSO_4$ and evaporated under vacuum. The residue is purified by silica gel chromatography using CH_2Cl_2/Hexane 95/5 as eluent.

Yield: 96 %.

MS (MH^+): 547/549/551.

1.1.8 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **38**:

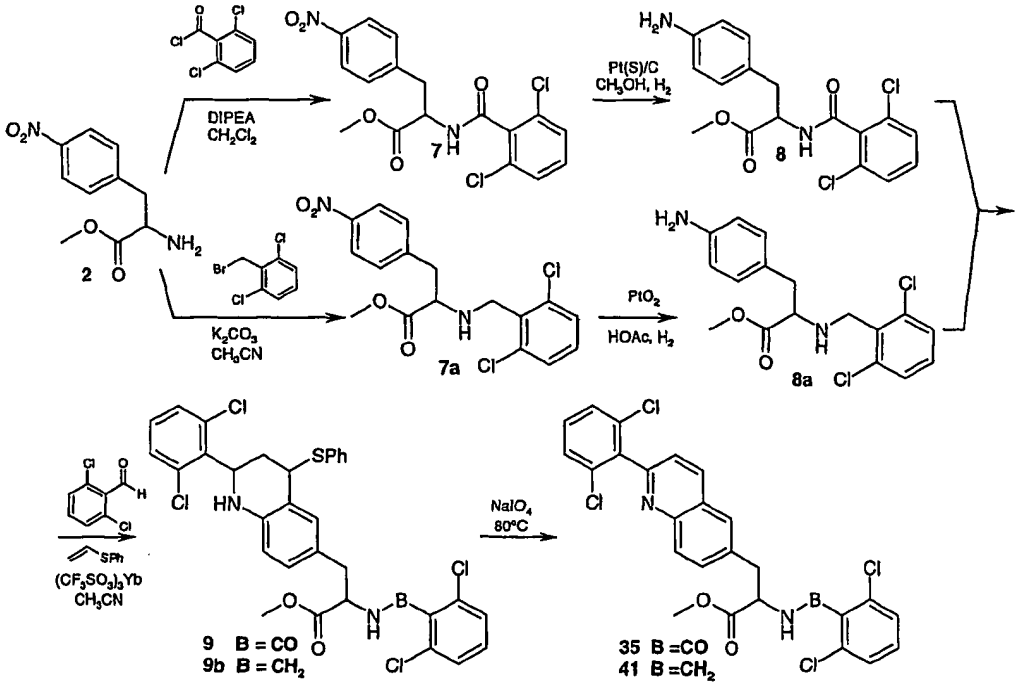
Methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **35** (0.2 g) is solubilized in CH_3CN/H_2O/NaOH 0.1N (4 ml / 0.22 ml / 3.65 ml). After 1 night at room temperature, 10 % $KHSO_4$ (9 ml) is added and CH_3CN is evaporated. The resulting aqueous phase is extracted two times with AcOEt (2 x 12 ml). The organic phase is washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The residue is purified by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ cc (90/10/1) as eluent.

Yield: 77 %.

MS (MH^+): 533/535/537.

1.2 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **35** and methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **41**:

Scheme 2:



1.2.1 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(4-nitrophenyl)propanoate **7**:

To a solution of methyl 2-amino-3-(4-nitrophenyl)propanoate **2** (9.5 g) in CH_2Cl_2 (40 ml) is added, at 0 °C, 2,6-dichlorobenzoyl chloride (7.71 g) dissolved in CH_2Cl_2 (40 ml). DIPEA (2 equ.) is then added dropwise to the mixture at 0 °C. The reaction is then

risen at RT and pH is brought to 7-8 by addition of DIPEA. The mixture is stirred for 2 h, then evaporated and the residue is placed in AcOEt (175 ml). The organic phase is washed one time with 5 % $NaHCO_3$ (150 ml), one time with water, one time with 10 % $KHSO_4$ (150 ml) and one time with brine, dried over $MgSO_4$ and evaporated. No further purification is needed.

Yield: 96 %.

MS (MH^+): 397/399/401.

1.2.2 Synthesis of methyl 2-[(2,6-dichlorobenzyl)amino]-3-(4-nitrophenyl)propanoate **7a**

To a solution of methyl 2-amino-3-(4-nitrophenyl)propanoate **2** (6 g) in CH_3CN (30 ml) is added, pulverized K_2CO_3 (11.095g), 2,6-dichlorobenzyl bromide (6.42 g). The mixture is stirred at RT for 6h then filtrated on decalite and evaporated. The residue is placed in CH_2Cl_2 (100 ml) and washed three time with water (100 ml) dried over $MgSO_4$ and evaporated. The residue is purified by silica gel chromatography using AcOEt/hexane 10/90 as eluent.

Yield: 74%.

MS (MH^+): 383/385/387.

1.2.3 Synthesis of methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzoyl)amino]propanoate **8**:

Methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(4-nitrophenyl)propanoate **7** (7 g) is solubilized in CH_3OH in presence of Pt(S)/C (5 % in weight). H_2 pressure is then applied at RT for 2 h. The catalyst is filtered over celite and the solvent is evaporated to give methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzoyl)amino]propanoate **8**.

Yield: 100 %.

MS (MH^+): 367/369/371.

1.2.4 Synthesis of methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzyl)amino]propanoate **8a**:

To methyl 2-[(2,6-dichlorobenzyl)amino]-3-(4-nitrophenyl)propanoate **7a** (8.2 g) solubilized in CH_3COOH in an ultrasonic bath is added PtO_2 hydrate (typical Pt content 79-84%) (0.02g). A H_2 pressure of 15 psi is then applied at RT and consummed after 5 min. An other H_2 pressure of 10 psis is then applied at RT and consummed after 5-10 min. A H_2 pressure of 10 psis is again applied at RT and a stabilization is observed after 5 min. The catalyst is filtered over celite under nitrogen and washed with CH_3COOH. The

solvent is evaporated. AcOEt (200ml) is added to the residue and this organic phase is washed three times with saturated $NaHCO_3$ (200 ml), dried over $MgSO_4$ and evaporated. The residue is purified by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ cc (99.75/0.25/0.025) as eluent.

Yield: 62 %.

MS (MH^+): 353/355/357.

1.2.5 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9**:

Methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfonyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9** is prepared according to the method described for compound **5** in scheme 1.

Yield: 81 %.

MS (MH^+): 659/661.

Methyl 2-(benzoylamino)-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9a**, methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9b** (MS (MH^+): 645/647/649), methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9c** (MS (MH^+): 651/653/655), methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[4-(phenylsulfanyl)-2-(1,3-thiazol-2-yl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9d** (MS (MH^+): 596/598/600), methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9e** (MS (MH^+): 658/660/662) and methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[4-(phenylsulfanyl)-2-(4-pyridinyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **9f** (MS (MH^+): 590/592/594) can be synthesized according to the same method.

1.2.6 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **35**:

Methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **35** is prepared according to the method described for compound **6** in scheme 1.

MS (MH^+): 547/549/551.

Methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **41** can be synthesized according to the same method.

MS (MH^+): 533/535/537.

1.3 Synthesis of 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl)carbonyl)amino]propanoic acid **90**.

1.3.1 Synthesis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate **45**:

Tert-butyl (2S)-2-{[(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1-piperidinecarboxylate **42** is deprotected with TFA (see 1.1.6) to give methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate **45**.

MS (MH^+): 486/488/490.

1.3.2 Synthesis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl)carbonyl)amino]propanoate **46**:

To methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate **45** (.2TFA salt) (0.965g) in CH_2Cl_2 (5ml) are added, at 0 C, DIPEA (0.97 ml) and p-toluenesulfonyl chloride (0.282 g) dissolved in CH_2Cl_2. The reaction is stirred at RT for one night, then the mixture is diluted with CH_2Cl_2. The organic phase is washed 3 times with a brine solution, dried over $MgSO_4$ and concentrated under vacuum. The residue is purified over silica gel using CH_2Cl_2/CH_3OH (99.5/0.5) as eluent to give methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl)carbonyl)amino]propanoate **46**.

Yield: 72 %.

MS (MH^+) : 640/642/644.

1.3.3 Synthesis of 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl)carbonyl)amino]propanoic acid **90**:

To 455 mg of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl)carbonyl)amino]propanoate **46** in CH_3OH (5 ml) are added 0.8 ml of 1 N NaOH and 1 ml of water. The solution is stirred at RT overnight, and 1 N HCl (0.8 ml) is added to obtain a weakly acidic pH. Methanol is then evaporated, and the solid obtained is filtered, washed with water and dried to give 3-[2-(2,6-

dichlorophenyl)-6-quinolinyl]-2-[(((2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl]carbonyl)amino]propanoic acid **90**.

Yield: 82 %.

MS (MH^+): 626/628/630.

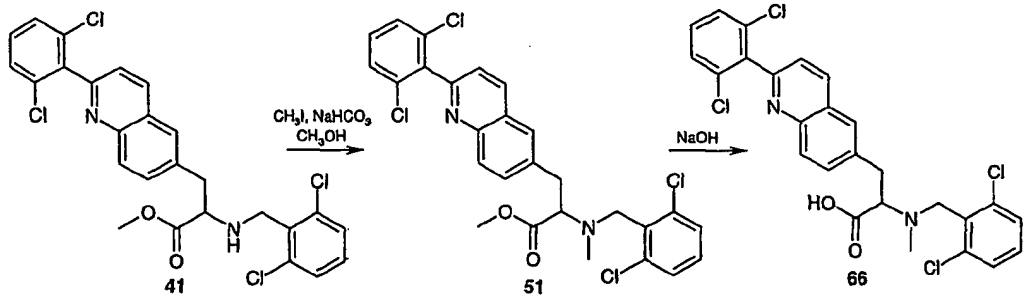
1.4 Synthesis of 2-{[(2,6-dichlorophenyl)(ethoxy)methylene]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **64**.

Compound **64** is synthesized according to Chem. Pharm. Bull. (1984), 32, (11), 4466-4477 starting from compound **35** followed by basic hydrolysis, as described for the transformation of compound **46** into compound **90**.

MS (MH^+): 561/563.

1.5 Synthesis of 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **66**.

Scheme 3:



1.5.1 Synthesis of methyl 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **51**:

To 100 mg of (methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate) **41** in CH_3OH (2.3 ml) are added, at 0 °C, $NaHCO_3$ (1 equ.) and CH_3I (1 equ.). The reaction is stirred for 1 h at 0 °C, and then at room temperature for 2 days. The solvent is evaporated and CH_2Cl_2 (10 ml) is added to the residue. The solution is washed with water, brine, again water and dried over $MgSO_4$, filtered and evaporated. Due to an incomplete reaction, the protocol is repeated using a tenfold excess of $NaHCO_3$ and CH_3I in MeOH (5 ml). After a similar work-up, the residue is purified by silica gel chromatography using hexane/AcOEt 90/10 as eluent to give methyl 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **51**.

Yield: 43 %.

MS (MH^+): 547/549/551.

1.5.2 Synthesis of 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **66**:

Hydrolysis of methyl 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **51** is performed as described in 1.3.3 and gives 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **66**.

Yield: 65 %.

MS (MH^+): 533/535/537.

1.6 Synthesis of 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-hydroxybenzoyl)amino]propanoic acid **71**:

Hydrolysis of methyl 2-{[2-(acetyloxy)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **70** as described in 1.3.3 gives 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-hydroxybenzoyl)amino]propanoic acid **71**.

Yield: 67 %.

MS (MH^+): 481/483/485.

1.7 Synthesis of 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **87**:

1.7.1 Synthesis of methyl 2-{[(2,6-dichloroanilino)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **52**:

To 0.62 g of methyl 2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **33** in CH_2Cl_2 (10 ml) are added 0.343 g of 2,6-dichlorophenyl isocyanate. The solution is stirred at RT and reduced to the half by evaporation. The solid residue is filtered and washed with CH_2Cl_2 and hexane to give a white powder that is recrystallised in hot CH_3CN. The compound is purified over silica gel using CH_2Cl_2/CH_3OH 99.5/0.5 as eluent. The obtained white powder is once more washed with CH_3CN to give methyl 2-{[(2,6-dichloroanilino)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **52**.

Yield: 36 %.

MS (MH^+): 562/564/566.

1.7.2 Synthesis of 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **87**.

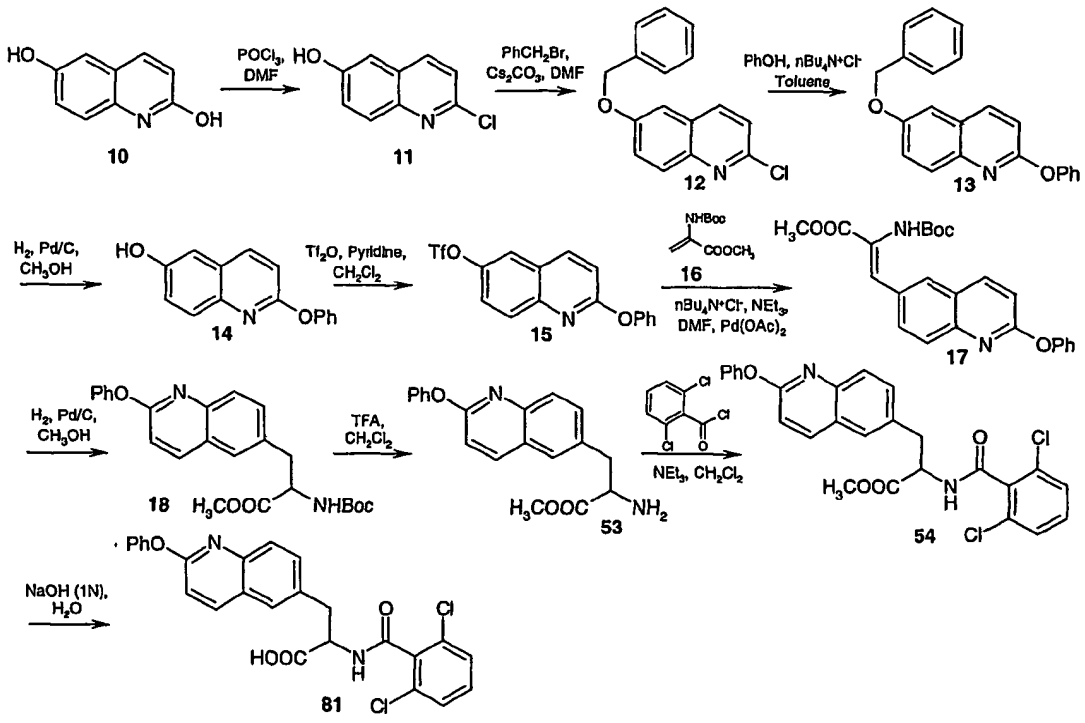
Hydrolysis of methyl 2-{[(2,6-dichloroanilino)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **52** as described in 1.3.3 gives 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **87**.

Yield: 58 %.

MS (MH^+): 548/550/552.

1.8 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl)propanoic acid **81**.

Scheme 4:



1.8.1 Synthesis of 2-chloro-6-quinolinol **11**:

A solution of 2,6-quinolinediol **10** (5 g) in $POCl_3$ (21 ml) and DMF (3.4 ml) is stirred for 12 h at room temperature, then heated for 1 h at 115 °C. The reaction is poured into water (100 ml) at 0 °C and neutralized with a 32 % aqueous NH_3 solution. The solid obtained by filtration is washed with acetone, and the resulting organic phase is evaporated to give 2-chloro-6-quinolinol **11** as a solid. No further purification is needed.

Yield: 98 %.

MS (MH^+): 180.

1.8.2 Synthesis of 6-(benzyloxy)-2-chloroquinoline **12**:

To a solution of 2-chloro-6-quinolinol **11** (5.45 g) in DMF (100 ml) is added, at 0 °C, cesium carbonate (11.9 g). After 15 minutes at 0 °C, benzyl bromide (4 ml) is added and the reaction is stirred for 12 h at room temperature. Water (100 ml) is then added and the solid obtained is filtered and washed with pentane. No further purification is needed. 6-(benzyloxy)-2-chloroquinoline **12** is obtained as a powder.

Yield: 94 %.

MS (MH^+): 170.

1.8.3 Synthesis of 6-(benzyloxy)-2-phenoxyquinoline **13**:

To a 50 % (w/w) NaOH solution (10.2 ml) is added phenol (0.697 g). After 50 minutes at room temperature, toluene (10.21 ml) and 6-(benzyloxy)-2-chloroquinoline **12** (2 g) and tetrabutyl ammonium (2.062 g) are added. The solution is stirred under argon at reflux for 24 h. Water (5 ml) is added and the solution is extracted with toluene (3 x 10 ml). The organic phases are dried over $MgSO_4$ and evaporated under vacuum. The residue is purified by silica gel chromatography using AcOEt/cyclohexane 20/80 as eluent. The obtained solid is dissolved in AcOEt and pentane is added; 6-(benzyloxy)-2-phenoxyquinoline **13** precipitates as a white powder.

Yield: 70 %.

MS (MH^+): 328.

Compounds described in table 1 can be synthesized according to the same method.

Table 1:

n°	IUPAC Name	MS (MH^+)
13a	6-(benzyloxy)-2-(4-chlorophenoxy)quinoline	362
13b	6-(benzyloxy)-2-methoxyquinoline	266
13c	6-(benzyloxy)-2-(2-methoxyphenoxy)quinoline	358
13d	6-(benzyloxy)-2-(2,6-dimethoxyphenoxy)quinoline	388
13e	6-(benzyloxy)-2-(2,6-dichlorophenoxy)quinoline	396/398

1.8.4 Synthesis of 2-phenoxy-6-quinolinol **14**:

To a solution of 6-(benzyloxy)-2-phenoxyquinoline **13** (0.862 g) in CH_3OH (10 ml) is added 10 % of palladium on C (10 %). The reaction is stirred under H_2 at room

temperature for 1 night. After filtration on celite and concentration, the residue is purified by silica gel chromatography using AcOEt/petroleum ether 10/90 as eluent to give compound 2-phenoxy-6-quinolinol **14** as an oil.

Yield: 61 %.

MS (MH^+): 238.

Compounds described in table 2 can be synthesized according to the same method.

Table 2:

n°	IUPAC Name	MS (MH^+)
14a	2-(4-chlorophenoxy)-6-quinolinol	272
14b	2-methoxy-6-quinolinol	176
14c	2-(2-methoxyphenoxy)-6-quinolinol	268
14d	2-(2,6-dimethoxyphenoxy)-6-quinolinol	298
14e	2-(2,6-dichlorophenoxy)-6-quinolinol	306/308

1.8.5 Synthesis of 2-phenoxy-6-quinolinyl trifluoromethanesulfonate **15**:

To a solution of 2-phenoxy-6-quinolinol **14** (0.562 g) in CH_2Cl_2 (20 ml) is added pyridine (0.6 ml) under Argon. After 15 minutes at 0 °C, trifluoromethanesulfonic anhydride (0.64 ml) is added. The reaction temperature is allowed to reach slowly room temperature. The reaction is stirred for 5 h and washed with a saturated solution of $NaHCO_3$. The solution is extracted with CH_2Cl_2 (3 x 10 ml). The organic phase is dried over $MgSO_4$ and evaporated under vacuum. The residue is purified by silica gel chromatography using AcOEt/petroleum ether 10/90 as eluent.

Yield: 87 %.

MS (MH^+): 370.

Compounds described in table 3 can be synthesized according to the same method.

Table 3:

n°	IUPAC Name	MS (MH^+)
15a	2-(4-chlorophenoxy)-6-quinolinyl trifluoromethanesulfonate	404
15b	2-methoxy-6-quinolinyl trifluoromethanesulfonate	308
15c	2-(2-methoxyphenoxy)-6-quinolinyl trifluoromethanesulfonate	400
15d	2-(2,6-dimethoxyphenoxy)-6-quinolinyl trifluoromethanesulfonate	430
15e	2-(2,6-dichlorophenoxy)-6-quinolinyl trifluoromethanesulfonate	438/440

1.8.6 Synthesis of methyl-2-N-(tert-butoxycarbonyl)-acrylate **16**:

To a solution of methyl 2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoate (7.19 g) in CH_2Cl_2 (15 ml) are added 3.04 ml of mesyl chloride. NEt_3 (13.64 ml) is then added at -50 °C, under Argon. After 45 minutes at -50 °C, the reaction warmed up to room temperature and stirred for 4 hours. The solution is poured into ice and the aqueous phase is extracted with CH_2Cl_2 (3 x 10 ml). The organic phases are dried over $MgSO_4$ and evaporated to dryness. The residue is purified by silica gel chromatography using AcOEt/cyclohexane 20/80 as eluent to give **16** as oil.

Yield: 93 %.

MS (MH^+): 202.

1.8.7 Synthesis of methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl)-2-propenoate **17**:

To a solution of 2-phenoxy-6-quinolinyl trifluoromethanesulfonate **15** (0.782 g) in DMF (20 ml) is added palladium acetate (0.0285 g). The solution is degassed with Argon for 30 minutes. Methyl-2-N-(tert-butoxycarbonyl)-acrylate **16** (1.065 g), tetrabutyl ammonium chloride (0.706 g) and NEt_3 (0.342 ml) are then added. The solution is heated at 90 °C for 2 h and then poured in ice. The aqueous phase is extracted with AcOEt (3 x 15 ml). The organic phases are dried over $MgSO_4$ and evaporated to dryness. The residue is purified by silica gel chromatography using AcOEt/ether petroleum 10/90 then 40/60 as eluent.

Yield: 91 %.

MS (MH^+): 421.

Compounds described in table 4 can be synthesized according to the same method.

Table 4:

n°	IUPAC Name	MS (MH^+)
17a	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(4-chlorophenoxy)-6-quinolinyl]-2-propenoate	455
17b	methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-methoxy-6-quinolinyl)-2-propenoate	359
17c	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]-2-propenoate	451
17d	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]-2-propenoate	481
17e	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]-2-propenoate	490

1.8.8 Synthesis of methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl) propanoate **18**:

To a solution of methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl)-2-propenoate **17** (1.053 g) in methanol (15 ml) is added 10 % of Pd over C (10 %). The reaction is stirred at room temperature under H_2 atmosphere overnight. After filtration over celite and concentration, the residue is purified by silica gel chromatography using AcOEt/ether petroleum 40/60 as eluent to give compound methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl) propanoate **18** as an oil.

Yield: 82 %.

MS (MH^+): 423.

Compounds described in table 5 can be synthesized according to the same method.

Table 5:

n°	IUPAC Name	MS (MH^+)
18a	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(4-chlorophenoxy)-6-quinolinyl]propanoate	457
18b	methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-methoxy-6-quinolinyl)propanoate	361
18c	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]propanoate	453
18d	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]propanoate	483
18e	methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]propanoate	491/493

1.8.9 Synthesis of methyl 2-amino-3-(2-phenoxy-6-quinolinyl)propanoate **53**:

A solution of 0.737 g of methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl) propanoate **18**, trifluoroacetic acid (1 ml) and a drop of anisole in CH_2Cl_2 (6 ml) is stirred at 0 °C under argon. The reaction temperature is allowed to reach slowly room temperature, and the solution is stirred at this temperature for 2 h. After concentration, the residue is diluted in AcOEt (6 ml) and the mixture is neutralized with $NaHCO_3$ (5 %). The aqueous phase is extracted with AcOEt (4 x 5 ml). The organic phases are dried over $MgSO_4$, filtered and concentrated. The obtained residue is purified over silica gel using (CH_2Cl_2/CH_3OH 90/10 + 5 % NEt_3) as eluent to give methyl 2-amino-3-(2-phenoxy-6-quinolinyl)propanoate **53** as an oil.

Yield: 85 %.

MS (MH^+): 322.

1.8.10 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl) propanoate **54**:

To a solution of methyl 2-amino-3-(2-phenoxy-6-quinolinyl)propanoate **53** (0.363 g) in CH_2Cl_2 (5 ml) under argon is added NEt_3 (0.937 ml). After 15 minutes, 2.6-dichlorophenylcarbonylchloride (0.241 ml) is added. The solution is stirred for 6 h at room temperature. After addition of $NaHCO_3$ (5 ml), the aqueous phase is extracted with CH_2Cl_2 (3 x 10 ml). The organic phases are dried over $MgSO_4$, filtered and concentrated. The obtained residue is purified over silica gel using AcOEt/petroleum ether 10/90 then 60/40 as eluent to give methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl) propanoate **54**.

Yield: 91 %.

MS (MH^+): 495.

1.8.11 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl)propanoic acid **81**:

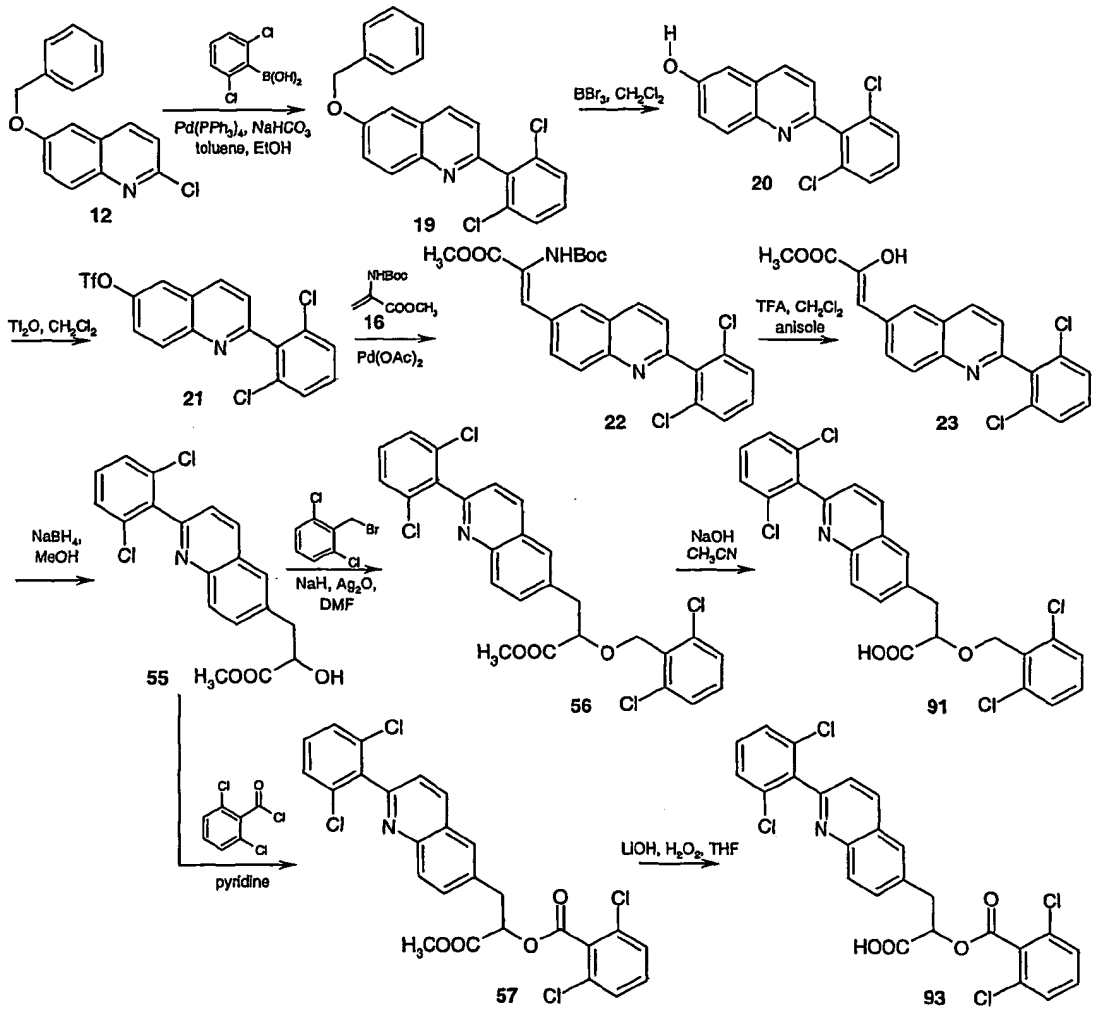
Methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl) propanoate **54** is added to a mixture of CH_3CN (10.99 ml), NaOH 1N (0.914 ml) and water (0.545 ml). The reaction is stirred at room temperature for 3 h. After addition of $KHSO_4$ (10 %, 22.4 ml), CH_3CN is evaporated under vacuum. The aqueous phase is extracted with AcOEt (2 x 5 ml). The organic phases are washed with brine, dried over $MgSO_4$and evaporated under vacuum. The resulting residue is washed with 5 ml of pentane to give 2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl)propanoic acid **81** as a white powder.

Yield: 82 %.

MS (MH^+): 481/483/485.

1.9 Synthesis of 2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **91** and 2-[(2,6-dichlorobenzoyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **93**.

Scheme 5:



1.9.1 Synthesis of 6-(benzyloxy)-2-(2,6-dichlorophenyl)quinoline **19**:

To a solution of 3g of 6-(benzyloxy)-2-chloroquinoline **12** in toluene (294ml) is added $Pd(PPh_3)_4$ (1 g). After 30 minutes, a solution of 2,6-dichlorophenylboronic acid (4.22 g) in methanol (186 ml) and 120 ml of a saturated aqueous solution of $NaHCO_3$ is added. The reaction is heated under reflux for 4h. After evaporation, the aqueous phase is extracted with AcOEt (3x20ml). The organic phases are washed with brine, dried over $MgSO_4$ and evaporated to dryness. The residue is purified over silica gel using AcOEt/petroleum ether 5/95 then 10/90 as eluent to give 6-(benzyloxy)-2-(2,6-dichlorophenyl)quinoline **19** as an oil.

Yield : 62 %.

MS (MH^+): 380.

1.9.2 Synthesis of 2-(2,6-dichlorophenyl)-6-quinolinol **20**:

To a solution of 6-(benzyloxy)-2-(2,6-dichlorophenyl)quinoline **19** (2.5 g) in CH_2Cl_2 (20 ml) are added, at 0 °C, 20 ml of BBr_3 (1 M in CH_2Cl_2). The solution is stirred for 1 h at room temperature. Water (20 ml) is added and the resulting solution is alkalinized with 1 N NaOH. The aqueous phase is extracted with AcOEt (3 x 20 ml). The organic phases are washed with brine, dried over $MgSO_4$ and evaporated. 2-(2,6-dichlorophenyl)-6-quinolinol **20** is obtained as a yellow solid and is used without further purification in the next step.

Yield: 100 %.

MS (MH^+): 290.

1.9.3 Synthesis of 2-(2,6-dichlorophenyl)-6-quinolinyl trifluoromethanesulfonate **21**:

To a solution of 2-(2,6-dichlorophenyl)-6-quinolinol **20** (1.9 g) in CH_2Cl_2 (20 ml) is added pyridine (1.6 ml) at room temperature. After 5 minutes, trifluoroacetic acid (1.7 ml) is added at 0 °C. The solution is stirred for 2 h at 0 °C and a saturated solution of $NaHCO_3$ (20 ml) is added. The aqueous phase is extracted with AcOEt (3 x 20 ml). The organic phases are washed with brine, dried over Na_2SO_4 and evaporated to dryness. The resulting solid **21** is used in the next step without further purification.

Yield: 100 %.

MS (MH^+): 422.

1.9.4 Synthesis of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-propenoate **22**:

To a solution of 2-(2,6-dichlorophenyl)-6-quinolinyl trifluoromethanesulfonate **21** (0.67 g) in DMF (15 ml) are added 0.8 g of freshly prepared methyl-2-N-(tert-butoxycarbonyl)-acrylate **16**, tetrabutylammonium (0.57 g) and NEt_3 (0.3 ml). The solution is degassed for 20 minutes and $Pd(OAc)_2$ (36 mg, 10 % mol) is added. The solution is heated at 90 °C for 3 h, then water (10 ml) is added. The aqueous phase is extracted with AcOEt (3 x 10 ml), and the organic phases are washed with water (2 x 10 ml), brine and dried over $MgSO_4$. After evaporation under vacuum, the residue is purified over silica gel using AcOEt/petroleum ether 20/80 as eluent.

Yield: 77 %.

MS (MH^+): 473.

1.9.5 Synthesis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxy-2-propenoate **23**:

To a solution of 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-propenoate **22** (0.48 g) in CH_2Cl_2 (2 ml) are added at 0 °C two drops of anisole and 1.6 ml of trifluoroacetic acid. The solution is stirred for 2 h and a solution of $NaHCO_3$ saturated is added to reach a basic pH. The aqueous phase is extracted with AcOEt (3 x 10 ml). The organic phases are washed with brine, dried over $MgSO_4$ and concentrated. The residue is washed with methanol to give methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxy-2-propenoate **23**.

Yield: 53 %.

MS (MH^+): 374.

1.9.6 Synthesis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxypropanoate **55**.

To a solution of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxy-2-propenoate **23** (0.38 g) in CH_3OH (2 ml) is added, at 0 °C, $NaBH_4$ (36 mg). The solution is stirred for 5h. A saturated solution of $NaHCO_3$ and then, a solution of 1 N NaOH are added until pH=11. The aqueous phase is extracted with AcOEt (3 x 10 ml). The organic phases are washed with brine, dried over $MgSO_4$ and concentrated. The residue is purified over silica gel using AcOEt/petroleum ether 30/70 then 35/65 as eluent to give methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxypropanoate **55**.

Yield: 65 %.

MS (MH^+): 377.

1.9.7 Synthesis of methyl 2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoate **56**.

To a solution of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxypropanoate **55** (0.159 g) and α-bromo-2,6-dichlorotoluene (1.05 g) in DMF (3.5 ml) is added 17 mg of NaH (60 % dispersion in mineral oil) and Ag_2O (0.102 g). The solution is stirred for 1 night at room temperature. A saturated solution of $NaHCO_3$ is added. The aqueous phase is extracted with AcOEt (3 x 10 ml). The organic phases are washed with water (2 x 10 ml), with brine and dried over $MgSO_4$. After concentration, the residue is purified twice over silica gel using AcOEt/petroleum ether 10/90 then 15/85 as eluent to give methyl 2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoate **56**.

Yield: 70 %.

MS (MH^+): 534.

1.9.8 Synthesis of 2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **91**:

A solution of methyl 2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoate **56** (0.123 g) and 1 N NaOH (0.236 ml) in a mixture of acetonitrile/water (3 ml / 0.14 ml) is stirred for 3 h at room temperature. After addition of a 10 % $KHSO_4$ solution (3 ml), the mixture is concentrated. The aqueous phase is extracted with AcOEt (3 x 10 ml). The organic phases are washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The residue is washed with CH_2Cl_2 and 2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **91** is obtained as a white powder.

Yield: 69 %.

MS (MH^+): 521.

1.9.9 Synthesis of 1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl 2,6-dichlorobenzoate **57**:

To a solution of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-hydroxypropanoate **55** (0.104 g) in pyridine (1 ml) is added 2,6-dichlorobenzoyl chloride (0.2 ml). The solution is stirred for 6 h at room temperature. A saturated solution of $NaHCO_3$ (10 ml) is added. The aqueous phase is extracted with AcOEt (3 x 10 ml). The organic phases are washed with brine, dried over $MgSO_4$ and evaporated. The residue is purified twice over silica gel using AcOEt/petroleum ether (10/90 to 20/80) as eluent.

Yield: 88 %.

MS (MH^+): 550.

1.9.10 Synthesis of 2-[(2,6-dichlorobenzoyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **93**:

To a solution of 1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl 2,6-dichlorobenzoate **57** (0.113 g) in 10 ml THF are added, at 0 °C, 1 ml of LiOH (1 M) and 0.5 ml of H_2O_2 (30 %). The solution is then stirred at room temperature for 18 h. After addition of 10 ml $KHSO_4$ (10 %), the THF is evaporated. The aqueous phase is extracted with AcOEt (3 x 10 ml). The organic phases are washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The residue is triturated in pentane to give 2-

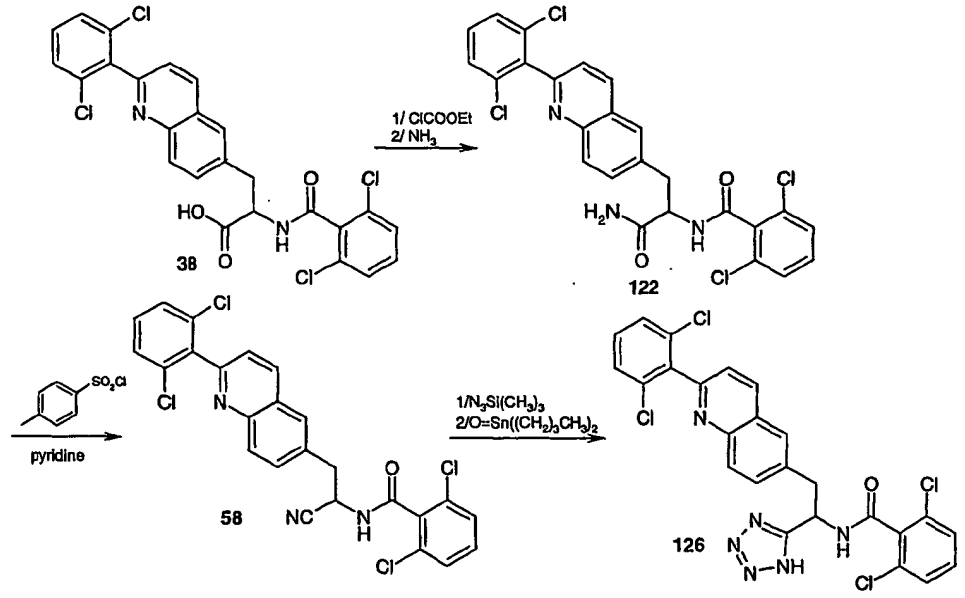
[(2,6-dichlorobenzoyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **93** as a white powder.

Yield: 93 %.

MS (MH^+): 534.

1.10 Synthesis of 2,6-dichloro-N-[2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(1H-tetraazol-5-yl)ethyl]benzamide **126**.

Scheme 6.



1.10.1 Synthesis of N-(2-amino-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide **122**.

2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **38** (2.12 g) in dry THF (15 ml) is cooled to -20 °C. NEt_3 (0.54 ml) and ethyl chloroformiate (0.37 ml) are added. The solution is stirred at this temperature for 20 minutes. The resulting solution is saturated with gaseous NH_3 at -30 °C. The mixture is allowed to reach room temperature. After one night, the residue is filtered and washed with THF, then dried under vacuum at 60 °C and purified over silica gel using CH_2Cl_2/CH_3OH (95/5) as eluent to give N-(2-amino-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide **122**.

Yield: 55 %.

MS (MH^+): 532/534/536.

1.10.2 Synthesis of 2,6-dichloro-N-{1-cyano-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}benzamide **58**.

To a solution of N-(2-amino-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide **122** (1.09 g) in pyridine (9 ml) is added p-toluenesulfonyl chloride (583 mg) at RT. The solution is stirred at 80 °C. After one night, 120 mg of p-toluenesulfonyl chloride are added again to the mixture at RT to drive the reaction to completion. The solution is heated at 80 °C for one additional day. The organic phases are evaporated, AcOEt and a small amount of CH_2Cl_2 are added. The organic phases are washed 3 times with water, one time with a solution of $NaHCO_3$, dried over $MgSO_4$ and evaporated to dryness. The residue so obtained was purified over silica gel using CH_2Cl_2/CH_3OH (99.25/0.75) as eluent to give 2,6-dichloro-N-{1-cyano-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}benzamide **58**.

Yield: 65 %.

MS (MH^+): 514/516/518.

1.10.3 Synthesis of 2,6-dichloro-N-[2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(1H-tetraazol-5-yl)ethyl]benzamide **126**.

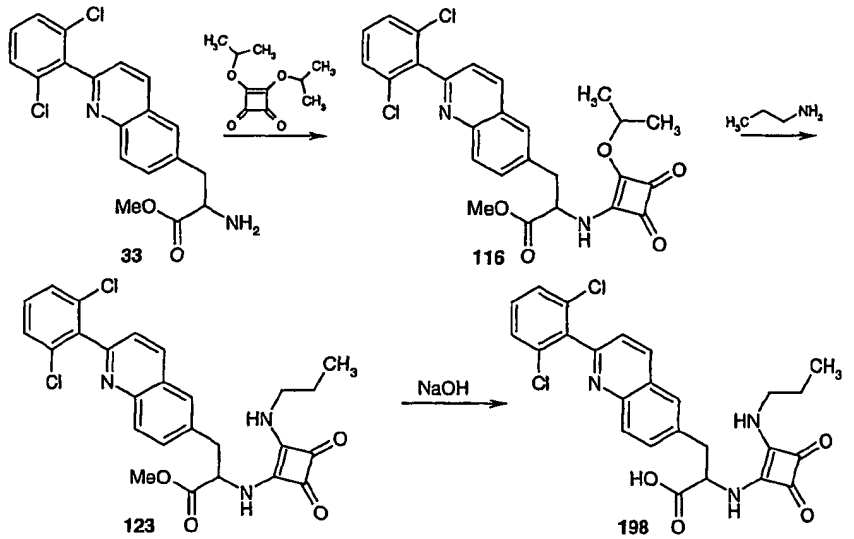
To 2,6-dichloro-N-{1-cyano-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}benzamide **58** (0.358 g) in toluene (5 ml) are added trimethylsilyl azide (184 µl) and dibutyltin oxide (17 mg). The solution is heated at reflux overnight, then evaporated under vacuum. The resulting residue is purified twice over silica gel using one time CH_2Cl_2/CH_3OH 85/15 as eluent and the second time $CH_2Cl_2/(CH_3OH$-10 % $NH_4OH)$ 85/15 to give 2,6-dichloro-N-[2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(1H-tetraazol-5-yl)ethyl]benzamide **126**.

Yield: 36 %.

MS (MH^+): 557/559/561.

1.11 Synthesis of 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoic acid **198**.

Scheme 7.



1.11.1 Synthesis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-isopropoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propanoate **116**.

To a solution of methyl 2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **33** (2TFA salt, 1.51 g) in CH_3OH (15 ml) cooled with an ice bath, are added 0.96 ml of DIPEA and 495.6 mg of 3.4-diisopropoxy-3-cyclobutene-1,2-dione. The solution is stirred overnight at RT. The solution is evaporated and the resulting residue is purified over silica gel using CH_2Cl_2/CH_3OH (99.2/0.8) as eluent to give methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-isopropoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propanoate **116**.

Yield: 57 %.

MS (MH^+): 513/515/517.

1.11.2 Synthesis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoate **123**.

To methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-isopropoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propanoate **116** (690 mg) in CH_3OH (20 ml) are added 132 µl of n-propylamine. After addition of DMF (15 ml), the solution is stirred at RT overnight. The evaporation of CH_3OH gives a DMF residue that is diluted in water (200 ml) and stirred overnight. The solid is filtered, washed with water then with MeOH, diluted in DMF, and n-propylamine (150 µl) is added to drive the reaction to completion. The solution is stirred at RT for 48 h, then poured into water. DMF is evaporated and the resulting solid is filtered, washed with water and dried. The product is purified by HPLC/MS (eluent:

CH_3CN/water/TFA, 8 minutes gradient from respectively 5/95/0.1 to 95/5/0.1). CH_3CN is evaporated and water is added to the residue. The resulting solid is filtered and dried to give methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoate **123**.

Yield: 10 %.

MS (MH^+): 513/515/517.

1.11.3 Synthesis of 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoic acid **198**.

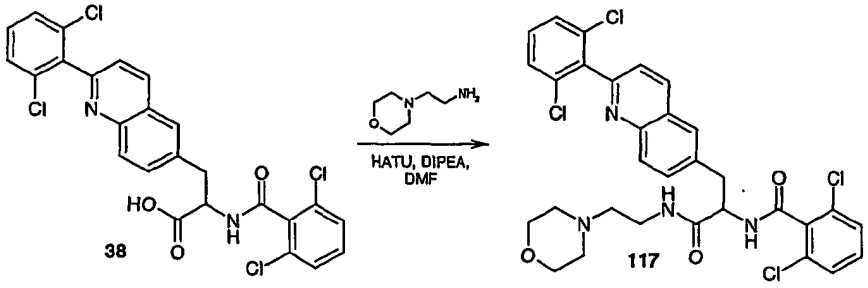
The basic hydrolysis of methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoate **123** into 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoic acid **198** follows the procedure described in 1.3.3.

Yield: 80 %.

MS (MH^+): 498/500/502.

1.12 Synthesis of 2,6-dichloro-N-(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-{[2-(4-morpholinyl)ethyl]amino}-2-oxoethyl)benzamide **117**.

Scheme 8.



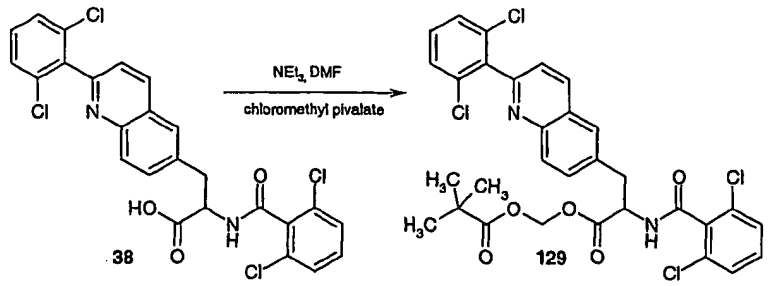
The transformation of 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **38** into 2,6-dichloro-N-(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-{[2-(4-morpholinyl)ethyl]amino}-2-oxoethyl)benzamide **117** follows the same conditions that the transformation of compound **33** into compound **35** (scheme 1).

Yield: 48 %.

MS (MH+): 645/647/649.

1.13 Synthesis of ({2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoyl}oxy)methyl pivalate **129**.

Scheme 9:



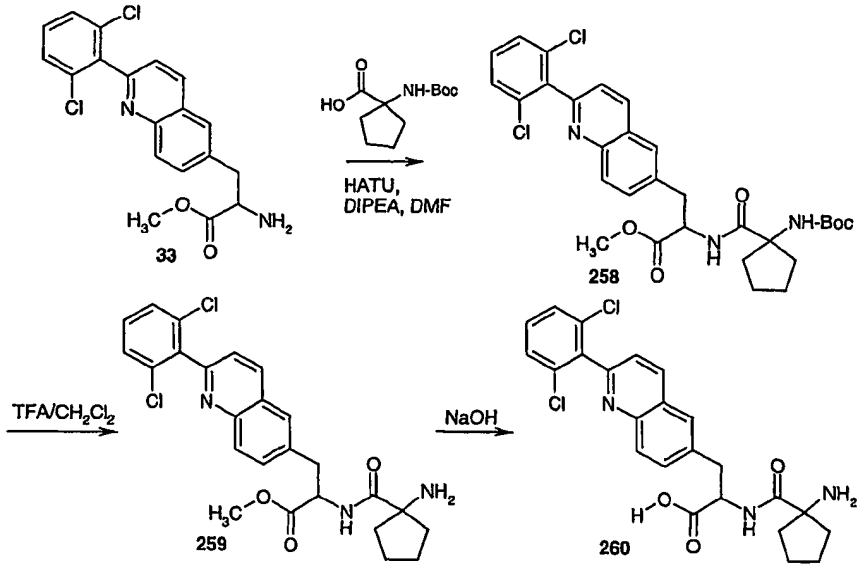
To 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **38** (534 mg) are added 195 µl of triethylamine and, after 15 minutes, 290 µl of chloromethyl pivalate. The solution is stirred at RT overnight and then poured in AcOEt. The organic phases are washed with water and brine, dried over $MgSO_4$ and concentrated. The resulting residue is purified over silica gel using CH_2Cl_2/C_2H_5OH 99/1 as eluent to give ({2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoyl}oxy)methyl pivalate **129**.

Yield: 85 %.

MS (MH^+): 647/649/651.

1.14. Synthesis of 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **260**.

Scheme 10



1.14.1. Synthesis of methyl 2-[({1-[(*tert*-butoxycarbonyl)amino]cyclopentyl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **258**.

Synthesis of methyl 2-[[(1-[(*tert*-butoxycarbonyl)amino]cyclopentyl]carbonyl]amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **258** from compound **33** follows the transformation of compound **33** into compound **35** as described in example 1.1.

Yield : 79 %.

MS (MH^+): 586/588/590.

1.14.2. Synthesis of methyl 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **259**.

Synthesis of methyl 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **259** from compound **258** follows the transformation of compound **6** into **33** as described is example 1.1.

Yield : 80 %.

MS (MH^+): 486/488/490.

1.14.3. Synthesis of 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **260**.

Synthesis of 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **260** from compound **259** follows the transformation of compound **35** into **38** as described is example 1.1.

Yield : 68 %.

MS (MH^+): 472/474/476.

1.15. Synthesis of tert-butyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **264**.

Compound **264** is synthesized from compound **38** according to method described in Takeda K., Synthesis (1994), 1063.

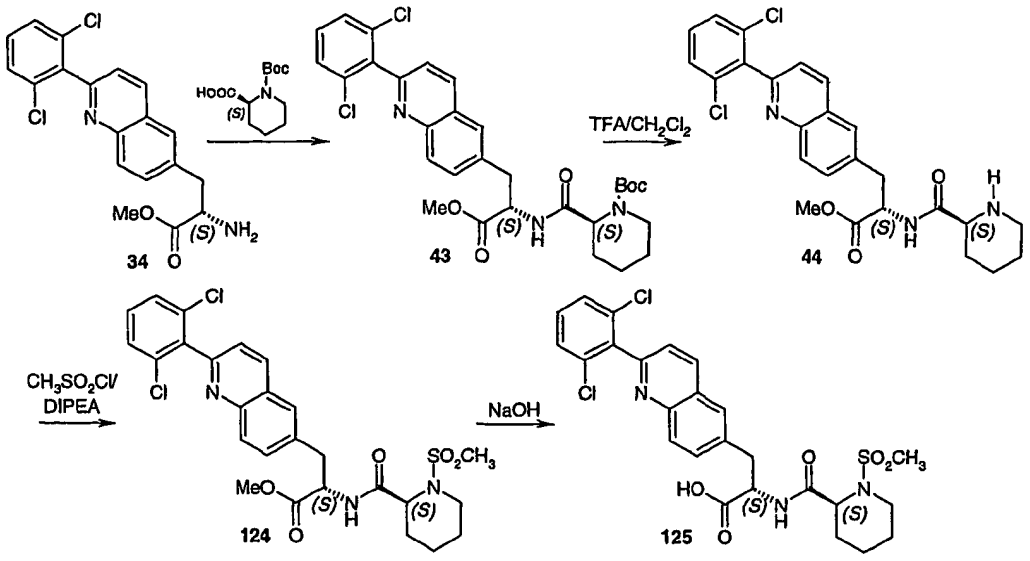
Yield : 16 %.

MS (MH^+): 589/591/593/595/597.

Example 2. Quinolinyl derivatives: stereospecific synthesis.

2.1 Synthesis of (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoic acid **125**.

Scheme 11.



2.1.1 Synthesis of tert-butyl (2S)-2-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1-piperidinecarboxylate **43**.

Synthesis of tert-butyl (2S)-2-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1-piperidinecarboxylate **43** from compound **34** follows the transformation of compound **33** into compound **35** as described in scheme 1.

Yield: 71 %.

MS (MH^+): 586/588/590.

2.1.2 Synthesis of methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate **44**.

The deprotection of tert-butyl (2S)-2-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1-piperidinecarboxylate **43** is performed according to the procedure described in 1.1.6 and gives methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate **44**.

Yield: 100 %.

MS (MH^+): 486/488/490.

2.1.3 Synthesis of methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoate **124**.

The mesylation of methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate **44** is performed according to the procedure described in 1.3.2. using mesylchloride instead of p-toluenesulfonyl chloride and gives methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{{[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoate **124**.

Yield: 45 %.

MS (MH^+): 564/566/568.

2.1.4 Synthesis of (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{{[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoic acid **125**.

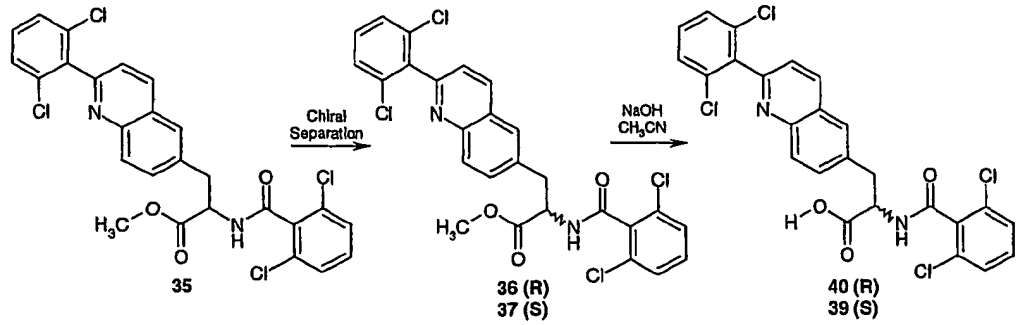
The basic hydrolysis of methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{{[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoate **124** is performed according to the procedure described in 1.3.3.

Yield: 78 %.

MS (MH^+): 550/552/554.

2.2 Synthesis of (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **40** and (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **39**.

Scheme 12



2.2.1 Synthesis of methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **36** and methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **37**:

Compounds **36** and **37** are obtained by chiral chromatography of racemic compound **35** (Chiralpak AD 100*500 nm, flow: 300 ml/min, length wave: 220 nm, Hexane mixture/ethanol 50/50 as eluent).

Compound **36**: second eluted.

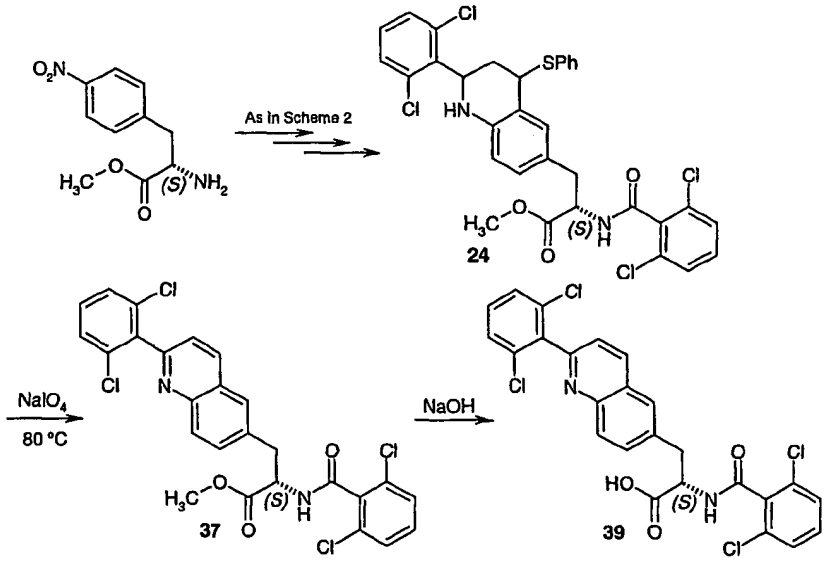
Compound **37**: first eluted.

2.2.2 Synthesis of (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **40** and (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **39**:

Hydrolysis at RT of methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **36** and methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **37** (as described in example 1.1 for the synthesis of compound **38**) gives respectively (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **40** and (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid **39**.

2.3 Synthesis of (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **39** according to scheme 13.

Scheme 13.

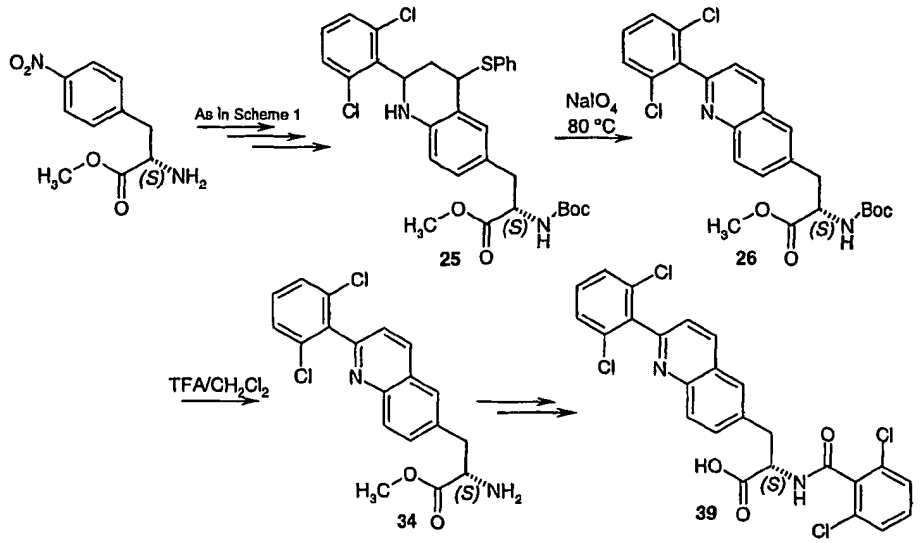


(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **39** can also be synthesised starting from (L)-p-nitro-Phe-OMe according to the synthesis described in scheme 2, involving methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **24** (MS (MH^+): 659/661) as intermediate.

(2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **40** can be synthesised according to the same procedure but starting from (D)-p-nitro-Phe-OMe, involving methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **24a** (MS (MH^+): 659/661) as intermediate.

2.4 Synthesis of (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **39** according to scheme 14.

Scheme 14.



(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **39** can also be synthesised starting from (L)-p-nitro-Phe-OMe according to the synthesis described in scheme 1, involving methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **25** (MS (MH^+): 587/589/591), methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **26** (MS (MH^+): 475/477/479) and methyl (2S)-2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **34** (MS (MH^+): 375/377/379) as intermediates.

Compounds described in table 6 can be synthesized as described for compound **25**.

Table 6:

n°	IUPAC Name	MS (MH^+)
25a	methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate	587/589/591
25b	methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate	579
25c	methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate	579
25d	methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethylphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate	547
25e	methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate	586/588/590

Compounds described in table 7 can be synthesized as described for compound **26**.

Table 7:

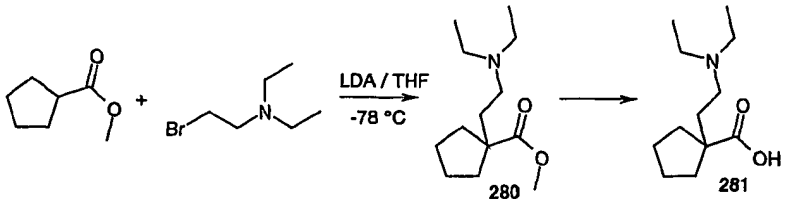
n°	IUPAC Name	MS (MH^+)
26a	methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	475/477/479
26b	methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate	467
26c	methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate	467
26d	methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoate	435
26e	methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate	476/478/480

(2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl] propanoic acid **40** can be synthesised according to the same procedure but starting from (D)-p-nitro-Phe-OMe, involving methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate **25a**, methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **26a** and methyl (2R)-2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **34a** (MS (MH^+): 375/377/379) as intermediates.

2.5 Synthesis of (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({1-[2-(diethylamino)ethyl]cyclopentyl}carbonyl)amino] propanoic acid **272** according to the same method as described in 2.4 (scheme 14).

1-[2-(diethylamino)ethyl]cyclopentanecarboxylic acid **281** used for the synthesis of (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({1-[2-(diethylamino)ethyl]cyclopentyl}carbonyl)amino] propanoic acid **272** is synthesised according to scheme 15.

Scheme 15:



2.5.1 Synthesis of methyl 1-[2-(diethylamino)ethyl]cyclopentanecarboxylate **280**:

To methyl cyclopentanecarboxylate (1 g) in THF (8 ml) at -61 °C is added a solution of 2M LDA (9.8 ml). The mixture is stirred at room temperature for 15 minutes, then 2-bromo-*N*,*N*-diethylethanamine hydrobromide (2.04 g) is added at -61 °C. The mixture is stirred for 5 minutes at this temperature, then at room temperature. The solution became yellow and was diluted with water (30 ml). The organic phase is extracted twice with a brine solution (30 ml). The pH of the organic phase is ajusted to 4 with 6N HCl. After decantation, the aqueous phase is extracted with CH_2Cl_2 (20 ml) and the pH of aqueous phase ajusted to 12 with 6 N NaOH. After decantation, the organic phase is dried over $MgSO_4$ and concentrated. The residue is treated with diethyl ether (10 ml) and the white solid is filtrated. Methyl 1-[2-(diethylamino)ethyl]cyclopentanecarboxylate **280** is obtained as a yellow liquid after concentration of the ether solution.

Yield: 79 %.

MS (MH^+): 228.

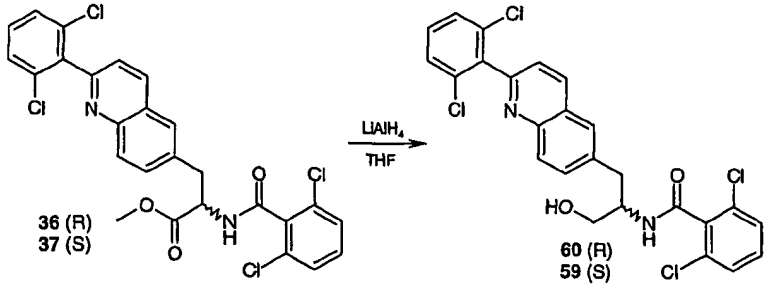
2.5.2 Synthesis of 1-[2-(diethylamino)ethyl]cyclopentanecarboxylic acid **281**

Synthesis of 1-[2-(diethylamino)ethyl]cyclopentanecarboxylic acid **281** from **280** follows the transformation of compound **35** into **38** as described is example 1.1.

Yield: 94 %.

MS (MH^+): 214.

2.6 Synthesis of 2,6-dichloro-N-[(1R)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide **60** and 2,6-dichloro-N-[(1S)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide **59**: Scheme 16.



2.6.1 Synthesis of 2,6-dichloro-N-[(1R)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide **60**.

To methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **36** (0,222 g) in THF (1 ml) is added, at 0 °C, $LiAlH_4$ (1,5 equ.). The solution is stirred at 0 °C for 1 hour. The reaction is quenched at -25 °C by successive additions of water (25 µl), 15 % NaOH (25 µl) and water (75 µl). After evaporation of THF under vacuum, AcOEt is added. The organic phases are washed with water, brine, dried over $MgSO_4$ and evaporated. The resulting residue is purified over silica gel using $CH_2Cl_2/CH_3OH/NH_4OH$ (99/1/0,1) as eluent to give 2,6-dichloro-N-[(1R)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide **60**.

Yield: 62 %.

MS (MH^+): 519/521/523.

2.6.2 Synthesis of 2,6-dichloro-N-[(1S)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide **59**.

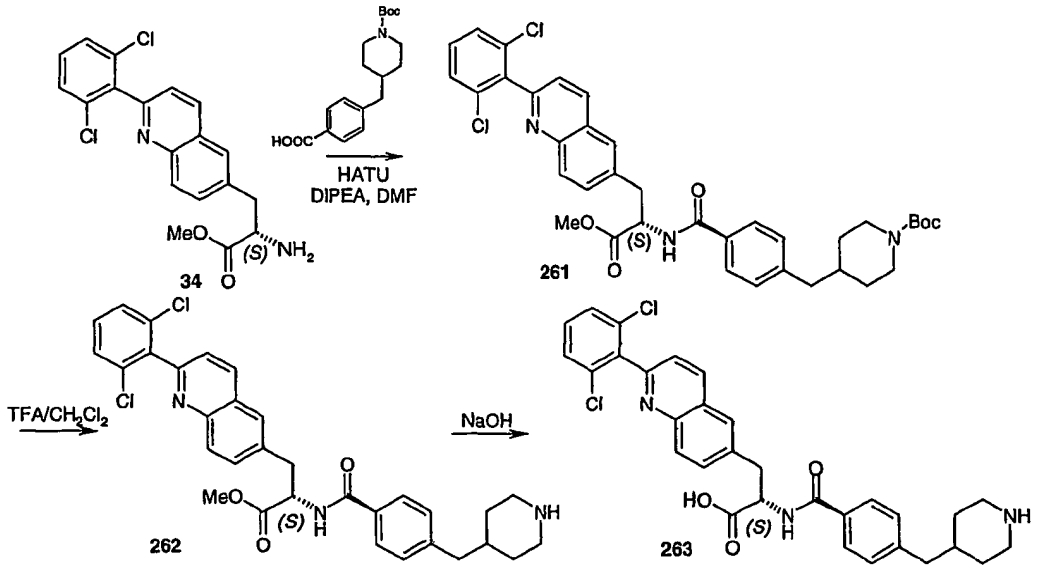
The synthesis of 2,6-dichloro-N-[(1S)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide **59** follows the procedure described for compound **60** using methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate **37** as starting material.

Yield: 48 %.

MS (MH^+): 519/521/523.

2.7 Synthesis of (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[[4-(4-piperidinylmethyl)benzoyl]amino]propanoic acid **263**.

Scheme 17.



2.7.1 Synthesis of *tert*-butyl 4-{4-[[((1*S*)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}benzyl)-1-piperidinecarboxylate **261**.

Synthesis of *tert*-butyl 4-{4-[[((1*S*)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}benzyl)-1-piperidinecarboxylate **261** follows the transformation of compound **33** into compound **258** as described is example 1.14.

Yield : 86 %.

MS (MH^+) : 676/678/680.

2.7.2 Synthesis of methyl (2*S*)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[4-(4-piperidinylmethyl)benzoyl]amino}propanoate **262**.

Synthesis of methyl (2*S*)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[4-(4-piperidinylmethyl)benzoyl]amino}propanoate **262** follows the transformation of compound **258** into compound **259** as described is example 1.14.

Yield : 87 %.

MS (MH+) : 576/578/580.

2.7.3 Synthesis of (2*S*)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[4-(4-piperidinylmethyl)benzoyl]amino}propanoic acid **263**.

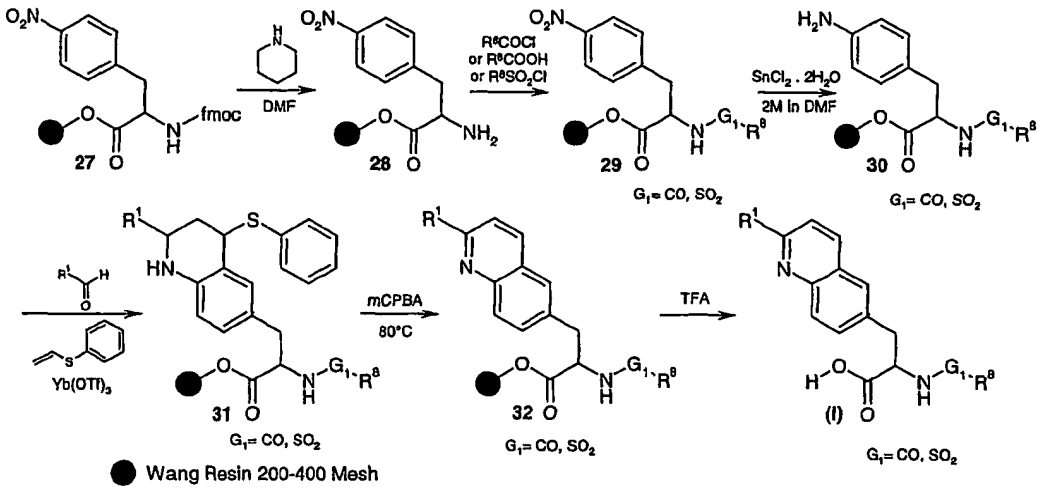
Synthesis of (2*S*)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[4-(4-piperidinylmethyl)benzoyl]amino}propanoic acid **263** follows the transformation of compound **259** into compound **260** as described is example 1.14.

Yield : 65 %.

MS (MH^+) : 562/564/566.

Example 3. Quinolinyl derivatives: combinatorial chemistry.

Scheme 18



Wang Resin: p-Benzyloxybenzyl Alcohol resin: The polymer matrix is copolystyrene -1 % DVB, 200-400 Mesh.

3.1 Synthesis of compound **28**.

The resin (Fmoc (L)-Phe (4-NO_2)-Wang Resin 200-400 Mesh (loading 0.75 mmol/g) is washed with MeOH, CH_2Cl_2 and DMF (3 times each, volume: 10 ml/g). The resin is prewashed with 20 % piperidine in DMF (10 ml/g) for 5 minutes and then filtered. A 20 % solution of piperidine in DMF (10 ml/g) is again added and stirring is maintained for 25 minutes. The resin is then filtered and washed 6 times with DMF and 3 times with CH_2Cl_2.

3.2 Synthesis of compound **29**.

3.2.1 Using R^8-COCl.

The resin (compound **28**) is washed 3 times with CH_2Cl_2 (volume: 10 ml/g). Ten equivalents of R^8-COCl in CH_2Cl_2 (10 ml/g) are then added, followed by 10 equivalents of DIPEA. Stirring is maintained for 2 h. The resin is filtered and washed with CH_2Cl_2, DMF and MeOH (3 times each, volume: 10 ml/g). Completion of the reaction is checked using a chloranil test on a small resin sample.

3.2.2 Using R^8-COOH.

The resin (compound **28**) is washed with CH_2Cl_2 followed by DMF (3 times each, volume: 10 ml/g). 10 equivalents of TBTU and 10 equivalents of HOBT (both as solids) are then added to the resin followed by R^8-COOH in DMF (10 ml/g). 30 equivalents of DIPEA are then added dropwise. Stirring is maintained for 2 h and the resin is filtered and washed 3 times with DMF, 3 times with CH_2Cl_2, 3 times with DMF and 3 times with MeOH (volume: 10 ml/g). Completion of the reaction is checked using a chloranil test on a small resin sample. If the reaction is not complete, the same procedure is started again but reaction is maintained overnight.

3.3 Synthesis of compound **30**.

The resin (compound **29**) is washed with CH_2Cl_2 followed by DMF (3 times each, volume: 10 ml/g). A 2M solution of $SnCl_2.2H_2O$ in DMF is then added (volume: 10 ml/g). Stirring is maintained 16 hours. The resin is then filtered and washed 6 times with DMF, 3 times with CH_2Cl_2, 3 times with CH_2Cl_2 + 10 % TEA, 6 times with CH_2Cl_2 and 3 times with MeOH (volume: 10 ml/g).

3.4 Synthesis of compound **31**.

The resin (compound **30**) is washed 3 times with CH_2Cl_2 (volume: 10 ml/g). Ten equivalents of aldehyde R^1CHO in CH_2Cl_2 (5 ml/g) are added to the resin and the slurry is stirred for 10 minutes. $Yb(OTf)_3$ (0.05 equivalents, 5 % mol) in CH_3CN (10 ml/g) is added, then 10 equivalents of phenyl vinyl sulfide, and the stirring is maintained for 20 hours. The resin is filtered and washed with MeOH, CH_2Cl_2, DMF, CH_2Cl_2 and MeOH (3 times each, volume: 10 ml/g).

3.5 Synthesis of compound **32**.

The resin (compound **31**) is washed 3 times with CH_2Cl_2 (10 ml/g). 1.3 equivalents of mCPBA in CH_2Cl_2 (10 ml/g) are subsequently added. After 1 hour of stirring the resin is filtered and washed with CH_2Cl_2, DMF, CH_2Cl_2 and MeOH (3 times each, 10 ml/g). The resin in DMF (10 ml/g) is then heated at 80 °C for 16 hours. The resin is then washed with DMF, CH_2Cl_2 and MeOH (3 times each, 10 ml/g).

3.6 Synthesis of compounds of formula I.

The resin (compound **32**, 500 mg/well) is dried under vacuum and the compounds of formula I are cleaved from by treating the resin 3 times with 5 ml solution of TFA/Water 95/5 during 15 minutes. After filtration, the resin is washed with the same

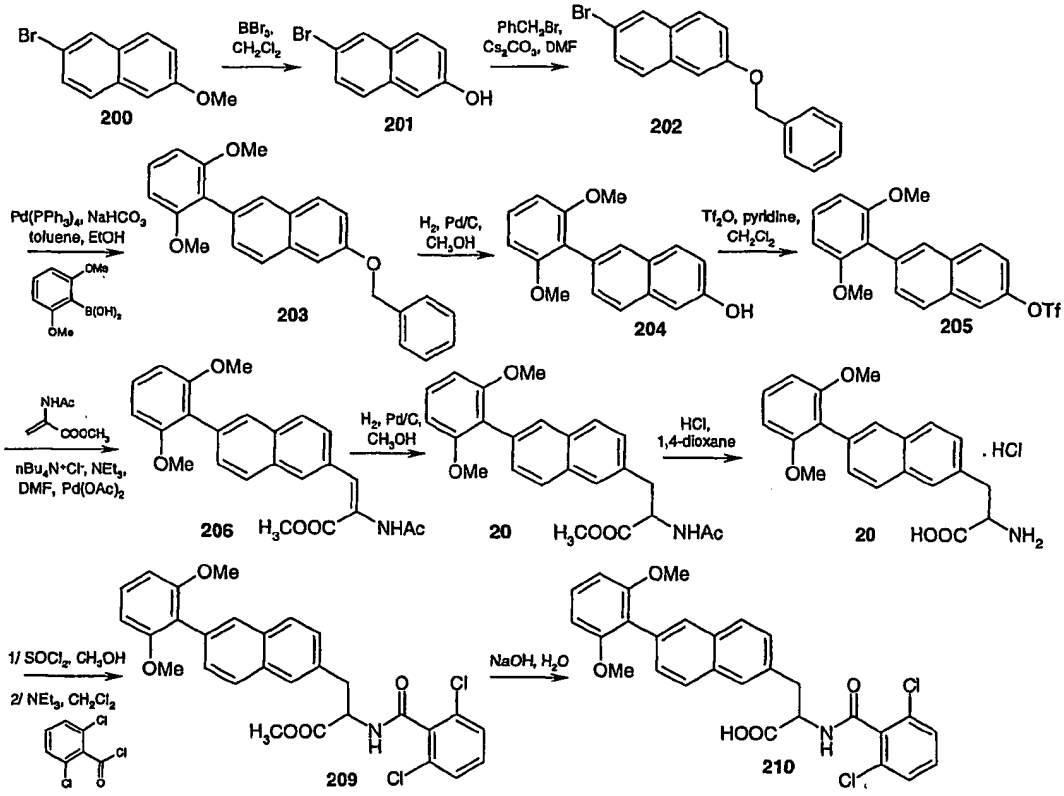
solvent. Solvent is removed at RT under vacuum using a Genevac apparatus and the product is purified by reverse phase chromatography (CH_3CN/water/0.1 % TFA).

Average overall yield: +/- 30 %.

Example 4. Naphthyl derivatives: racemic synthesis.

4.1 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid **210**.

Scheme 19



4.1.1 Synthesis of 6-bromo-2-naphthol **201**:

Deprotection of 2-bromo-6-methoxynaphthalene **200** as described in 1.9.2 gives 6-bromo-2-naphthol **201**.

Yield: 94 %.

MS (MH^+): 227.

4.1.2 Synthesis of 2-(benzyloxy)-6-bromonaphthalene **202**:

Protection of 6-bromo-2-naphthol **201** as described in 1.8.2 gives 2-(benzyloxy)-6-bromonaphthalene **202**.

Yield: 98 %.

MS (MH^+): 313.

4.1.3 Synthesis of 2-(benzyloxy)-6-(2,6-dimethoxyphenyl)naphthalene **203**:

Reaction of 2-(benzyloxy)-6-bromonaphthalene **202** with 2,6-dimethoxyboronic acid as described in 1.9.1 gives 2-(benzyloxy)-6-(2,6-dimethoxyphenyl)naphthalene **203**.

Yield: 95 %.

MS (MH^+): 370.

4.1.4 Synthesis of 6-(2,6-dimethoxyphenyl)-2-naphthol **204**:

Deprotection of 2-(benzyloxy)-6-(2,6-dimethoxyphenyl)naphthalene **203** as described in 1.8.4 gives 6-(2,6-dimethoxyphenyl)-2-naphthol **204**.

Yield: 92 %.

MS (MH^+): 281.

4.1.5 Synthesis of 6-(2,6-dimethoxyphenyl)-2-naphthyl trifluoromethanesulfonate **205**:

Reaction of 6-(2,6-dimethoxyphenyl)-2-naphthol **204** with trifluoromethanesulfonic anhydride as described in 1.8.5 gives 6-(2,6-dimethoxyphenyl)-2-naphthyl trifluoromethanesulfonate **205**.

Yield: 80 %.

MS (MH^+): 413.

4.1.6 Synthesis of methyl (2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-propenoate **206**:

Reaction of 6-(2,6-dimethoxyphenyl)-2-naphthyl trifluoromethanesulfonate **205** with methyl-2-N-acetyl-acrylate as described in 1.8.7 gives methyl (2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-propenoate **206**.

Yield: 88 %.

MS (MH^+): 406.

4.1.7 Synthesis of methyl 2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **207**:

Hydrogenation of methyl (2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-propenoate **206** as described in 1.8.8. gives methyl 2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **207**.

Yield: 99 %.

MS (MH^+): 408.

4.1.8 Synthesis of 2-amino-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid hydrochloride **208**:

To a solution of 1.4-dioxane (1 ml) are added successively 6 N HCl (3 ml) and methyl 2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **207** (0.135 g). The solution is stirred and heated at reflux for 4 hours, then cooled, and diethyl ether (5 ml) is added. The aqueous phase is extracted with diethyl ether (35 ml). The organic phase is concentrated under vacuum. The resulting residue is dried overnight under hight pression to give 2-amino-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid hydrochloride **208**.

Yield: 81 %.

MS (MH^+): 352.

4.1.9 Synthesis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **209**:

Esterification of 2-amino-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid hydrochloride **208** as described in 1.1.1 followed by acylation as described in 1.8.10 gives methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **209**.

Yield: 72 %.

MS (MH^+): 538/540/542.

4.1.10 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid **210**:

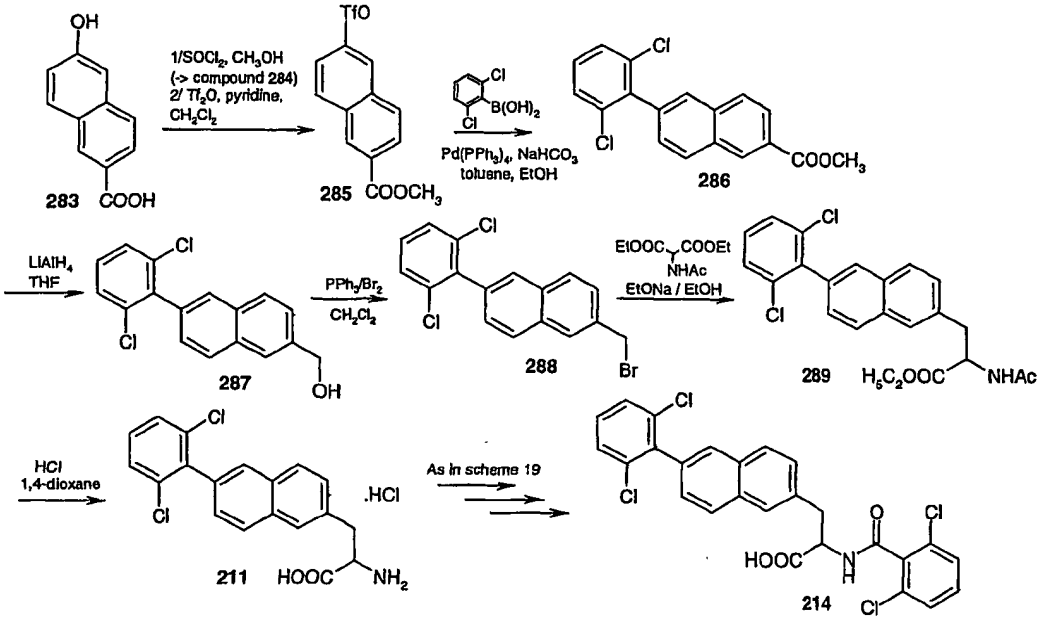
Hydrolysis of methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **209** as described in 1.8.11 gives 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid **210**.

Yield: 64 %.

MS (MH^+): 524/526/528.

4.2 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid **214**.

Scheme 20



4.2.1 Synthesis of methyl 6-hydroxy-2-naphthoate **284**:

Reaction of 6-hydroxy-2-naphthoic acid **283** with $SOCl_2$ as described in 1.1.1. gives methyl 6-hydroxy-2-naphthoate **284**.

Yield: 97 %.

MS (MH^+): 202.

4.2.2 Synthesis of methyl 6-{[(trifluoromethyl)sulfonyl]oxy}-2-naphthoate **285**:

Reaction of methyl 6-hydroxy-2-naphthoate **284** with trifluoromethanesulfonic anhydride as described in 4.1.5. gives methyl 6-{[(trifluoromethyl)sulfonyl]oxy}-2-naphthoate **285**.

Yield: 90 %.

MS (MH^+): 334.

4.2.3 Synthesis of methyl 6-(2,6-dichlorophenyl)-2-naphthoate **286**:

Reaction of methyl 6-{[(trifluoromethyl)sulfonyl]oxy}-2-naphthoate **285** as described in example 4.1.3. gives methyl 6-(2,6-dichlorophenyl)-2-naphthoate **286**.

Yield: 93 %.

MS (MH^+): 331.

4.2.4 Synthesis of [6-(2,6-dichlorophenyl)-2-naphthyl]methanol **287**:

Reaction of methyl 6-(2,6-dichlorophenyl)-2-naphthoate **286** as described in 2.5.1. gives [6-(2,6-dichlorophenyl)-2-naphthyl]methanol **287.**

Yield: 98 %.

MS (MH^+): 303.

4.2.5 Synthesis of 2-(bromomethyl)-6-(2,6-dichlorophenyl)naphthalene **288**:

To a solution of PPh_3 (0.251 g) in CH_2Cl_2 (1 ml) is added drop by drop, at 0°C, a solution of bromine (0.049 ml) in CH_2Cl_2 (1 ml). After 30 min, [6-(2,6-dichlorophenyl)-2-naphthyl]methanol **287** (0.242 g) is added. The mixture is stirred, under argon, at RT for 6h. Water (2 ml) is added. The aqueous phase is extracted with CH_2Cl_2 (3 x 5 ml). The organic phases are dried over $MgSO_4$ and evaporated under vacuum. The residue is purified by silica gel chromatography using AcOEt/cyclohexane 40/60 as eluent.

Yield: 95 %.

MS (MH^+): 366.

4.2.6 Synthesis of ethyl 2-(acetylamino)-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoate **289**:

To a solution of Na (0.092 g) in ethanol (5 ml) is added diethyl 2-(acetylamino)malonate (0.870 g). The mixture is stirred for 1h. A solution of 2-(bromomethyl)-6-(2,6-dichlorophenyl)naphthalene **288** (0.978 g) in ethanol (5 ml) is added, under argon. The mixture is stirred under reflux for 5h. After addition of water (5 ml), the solution is concentrated under vacuum and then diluted with AcOEt (5 ml). The aqueous phase is extracted with AcOEt (3 x 15 ml). The organic phases are dried over $MgSO_4$, filtrated and evaporated under vacuum. The residue is purified by silica gel chromatography using AcOEt/cyclohexane 20/80 then (40/60) as eluent.

Yield: 54 %.

MS (MH^+): 430.

4.2.7 Synthesis of 2-amino-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid hydrochloride **211**:

Reaction of ethyl 2-(acetylamino)-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoate **289** with HCl as described in 4.1.8. gives 2-amino-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid hydrochloride **211.**

Yield: 91 %.

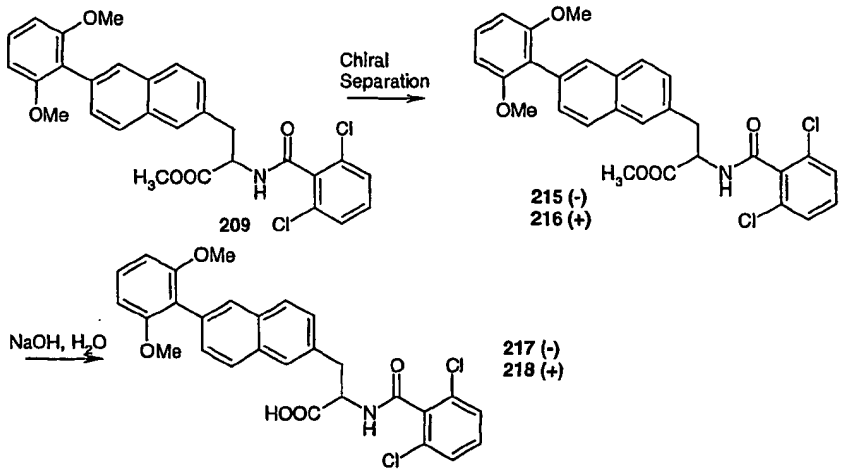
MS (MH^+): 396.

4.2.8 Synthesis of 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid **214**:

2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid **214** can be synthesised starting from 2-amino-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid hydrochloride **211** according to the synthesis described in scheme 19.

Example 5. Naphthyl derivatives : stereospecific synthesis. Synthesis of (-)- and (+)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid **217** and **218**.

Scheme 21



5.1 Synthesis of (-) and (+) methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **215** and **216**

Synthesis of (-) and (+) methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate **215** and **216** follows the transformation of compound **35** into **36** and **37** as described is example 2.2.

MS (MH^+) : 538/540/542.

5.2. Synthesis of (-) and (+) 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid **217** and **218.**

According to the transformation of compounds **36** and **37** into **40** and **39** as described in example 2.2.

Yield : respectively 83 % and 84 %.

MS (MH^+) : 524/526/228.

Compounds described in table 8 can be synthesized according to one of these methods.

In the table, the stereochemical information is contained in the two columns headed 'configuration data'. The second column indicates whether a compound is a pure configuration isomer or enantiomer (Pure), a racemate (Rac) or is a mixture of two or more stereoisomers, possibly in unequal proportions (Mixt). The first column contains the stereochemical assignment for each recognised center, following the IUPAC numbering used in the preceding column. A number alone indicates the existence of both configurations at that center. A number followed by 'R' or 'S' indicates the known absolute configuration at that center. A number followed by '§' indicates the existence of only one but unknown absolute configuration at that center. The letter (A, B, C, D) in front is a way of distinguishing the various configuration isomers, enantiomers or racemates of the same structure.

Table 8:

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
33	2	Rac	methyl 2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		375/377/379
34	2S	Pure	methyl (2S)-2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		375/377/379
34a	2R	Pure	methyl (2R)-2-amino-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		375/377/379
35	2	Rac	methyl 2-{[(2,6-dichlorophenyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		547/549/551
36	2R	Pure	methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	+52.77 (CH_3CN, 1 %)	547/549/551
37	2S	Pure	methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	-51.95 (CH_3CN, 1 %)	547/549/551
38	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		533/535/537
39	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	-61.92 (CH_3OH, 1 %)	533/535/537
40	2R	Pure	(2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	+57.25 (CH_3OH, 1 %)	533/535/537
41	2	Rac	methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		533/535/537
42	2S,1	Mixt	tert-butyl (2S)-2-{[(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1-piperidinecarboxylate		586/588/590

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
43	2S,1S	Pure	tert-butyl (2S)-2-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1-piperidinecarboxylate		586/588/590
44	2S,2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate		486/488/490
45	2,2S	Mixt	methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2S)-piperidinylcarbonyl]amino}propanoate		486/488/490
46	2,2S	Mixt	methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoate		640/642/644
47	2	Rac	methyl 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		581/583/585
48	2S,3aS,7aS,2	Mixt	tert-butyl (2S,3aS,7aS)-2-{[(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}octahydro-1H-indole-1-carboxylate		626/628/630
49	2,2S,3aS,7aS	Mixt	methyl 2-{[(2S,3aS,7aS)-octahydro-1H-indol-2-ylcarbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		526/528/530
50	2,2S,3aS,7aS	Mixt	methyl 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		680/682/684
51	2	Rac	methyl 2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		547/549/551
52	2	Rac	methyl 2-{[(2,6-dichloroanilino)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		562/564/566
53	2	Rac	methyl 2-amino-3-[2-(phenyloxy)-6-quinolinyl]propanoate		322

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
54	2	Rac	methyl 2-{[(2,6-dichlorophenyl)carbonyl]amino}-3-[2-(phenyloxy)-6-quinolinyl]propanoate		495
55	2	Rac	methyl 3-[2-(2,6-dimethylphenyl)-6-quinolinyl]-2-hydroxypropanoate		377
56	2	Rac	methyl 2-{[(2,6-dichlorophenyl)methyl]oxy}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		534
57	2	Rac	1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-(methyloxy)-2-oxoethyl 2,6-dichlorobenzoate		550
58	1	Rac	2,6-dichloro-N-{1-cyano-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}benzamide		514/516/518
59	1S	Pure	2,6-dichloro-N-[(1S)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide	-36.25 (CH_3OH, 1 %)	519/521/523
60	1R	Pure	2,6-dichloro-N-[(1R)-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(hydroxymethyl)ethyl]benzamide	+68.10 (CH_3OH, 1 %)	519/521/523
61	2	Rac	2-(benzoylamino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		465/467/469
62	2	Rac	2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		519/521/523
63	2,4R	Mixt	2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		518/520/522
64	2	Rac	2-{[(2,6-dichlorophenyl)(ethoxy)methylene]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		561/563
65	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid		525/527/529
66	2	Rac	2-[(2,6-dichlorobenzyl)(methyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		533/535/537

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
67	2	Rac	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid		525/527/529
68	2	Rac	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethylbenzoyl)amino]propanoic acid		493/495/497
69	2	Rac	2-{[(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}benzyl benzoate		613/615/617
70	2	Rac	methyl 2-{[2-(acetyloxy)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		537/539/541
71	2	Rac	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-hydroxybenzoyl)amino]propanoic acid		481/483/485
72	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-(2-methoxy-6-quinolinyl)propanoic acid		419/421/423
73	2	Rac	2-(benzoylamino)-3-(2-phenyl-6-quinolinyl)propanoic acid		397
74	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenyl-6-quinolinyl)propanoic acid		465/467/469
75	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(1,3-thiazol-2-yl)-6-quinolinyl]propanoate		486/488/490
76	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(4-pyridinyl)-6-quinolinyl]propanoic acid		466/468/470
77	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(1,3-thiazol-2-yl)-6-quinolinyl]propanoic acid		472/474/476
78	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid		534/536

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
79	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate		548/550/552
80	2	Rac	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-difluorobenzoyl)amino]propanoic acid		501/503/505
81	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-(2-phenoxy-6-quinolinyl)propanoic acid		481/483/485
82	2S,4R	Pure	methyl (2S)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate	-15.96 (CH_3OH, 1 %)	524
83	2S	Pure	methyl (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	-57.25 (CH_3CN, 1 %)	591/593/595
84	1R,3S,1	Mixt	(1R,3S)-3-{[(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1,2,2-trimethylcyclopentanecarboxylic acid		557/559/561
85	2S	Pure	(2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	-68.63 (CH_3CN, 1 %)	513/515/517
86	2S	Pure	(2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	-50.32 (CH_3CN, 1 %)	577/579/581
87	2	Rac	2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		548/550/552
88	2R (90 %) 2S (10 %)	Mixt	(2R)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid (90 %) (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid (10 %)	ee: 82 %	567/569/571

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
89	2S	Pure	(2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	ee: 98 %	567/569/571
90	2,2S	Mixt	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid		626/628/630
91	2	Rac	2-[(2,6-dichlorobenzyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		521
92	1R,3S,1	Mixt	(1R,3S)-3-[({1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid		543/545/547
93	2	Rac	2-[(2,6-dichlorobenzoyl)oxy]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		534
94	2S	Pure	(2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid	ee : > 95 %	478
95	2S	Pure	(2S)-2-[(2,6-difluorobenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid	ee : > 95 %	501
96	2S	Pure	(2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-difluorobenzoyl)amino]propanoic acid	ee : > 95 %	485
97	2S	Pure	(2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid	ee : > 95 %	513
98	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid	ee : > 95 %	510
99	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid	ee : > 95 %	533

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
100	2S	Pure	(2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid	ee : > 95 %	517
101	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid	ee : > 95 %	545
102	2S	Pure	(2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid	ee : > 95 %	490
103	2S	Pure	(2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid	ee : > 95 %	513
104	2S	Pure	(2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid	ee : > 95 %	497
105	2S	Pure	(2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid	ee : > 95 %	525
106	2S	Pure	(2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-nitrophenyl]-6-quinolinyl}propanoic acid	ee : > 95 %	554
107	2S	Pure	(2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid	ee : > 95 %	577
108	2S	Pure	(2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid	ee : > 95 %	561
109	2S	Pure	(2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid	ee : > 95 %	589
110	2S,4R	Pure	(2S)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid	ee : > 98 %	510

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
111	2,2S,3aS,7aS	Mixt	2-[{[(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		666/668/670
112	2S,2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate	-3.54 (DMSO, 1 %)	487/489/491
113	2S,2R	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate	-13.7 (DMSO, 1 %)	487/489/491
114	2S,2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	+13.54 (DMSO, 1 %)	473/475/477
115	2S,2R	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	+5.77 (DMSO, 1 %)	473/475/477
116	2	Rac	methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-isopropoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propanoate		513/515/517
117	1	Rac	2,6-dichloro-N-(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-{[2-(4-morpholinyl)ethyl]amino}-2-oxoethyl)benzamide		645/647/649
118	1	Rac	2,6-dichloro-N-(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxo-2-{[2-(1-pyrrolidinyl)ethyl]amino}ethyl)benzamide		629/631/633
119	1	Rac	2,6-dichloro-N-(1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-{[2-(dimethylamino)ethyl]amino}-2-oxoethyl)benzamide		603/605/607
120	1	Rac	2,6-dichloro-N-[1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-(methylamino)-2-oxoethyl]benzamide		546/548/550
121	1	Rac	2,6-dichloro-N-[1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-(hydroxyamino)-2-oxoethyl]benzamide		548/550/552

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
122	1	Rac	N-(2-amino-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide		532/534/536
123	2	Rac	methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoate		513/515/517
124	2S,2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoate	-1.55 (CH_2Cl_2, 1 %)	564/566/568
125	2S,2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoic acid	+29.41 (CH_2Cl_2, 1 %)	550/552/554
126	1	Rac	2,6-dichloro-N-[2-[2-(2,6-dichlorophenyl)-6-quinolinyl]-1-(1H-tetraazol-5-yl)ethyl]benzamide		557/559/561
127	2	Rac	methyl 2-{[(6-amino-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		495/497/499
128	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]propanoate		525
129	2	Rac	({2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoyl}oxy)methyl pivalate		647/649/651
130	2S,4R	Pure	methyl (2S)-2-({[(4R)-3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	+10.51 (CH_3OH, 1 %)	564/566/568
131	**		2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-chlorophenyl)-6-quinolinyl]propanoic acid		632
132	**		3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[(2,6-dichlorophenyl)sulfonyl]amino}propanoic acid		458
133	**		3-[2-(3,4-dichlorophenyl)-6-quinolinyl]-2-{[(2,6-dichlorophenyl)sulfonyl]amino}propanoic acid		569

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
134	**		3-[2-(2-bromophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid		543
135	**		3-[2-(2-bromophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid		636
136	**		2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-bromophenyl)-6-quinolinyl]propanoic acid		676
137	**		3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}-2-[(2,6-dichlorobenzoyl)amino]propanoic acid		567
138	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid		547
139	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid		611
140	**		3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid		660
141	**		2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid		700
142	**		3-(2-cyclohexyl-6-quinolinyl)-2-[(2,6-dichlorobenzoyl)amino]propanoic acid		471
143	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-(2-cyclohexyl-6-quinolinyl)propanoic acid		505
144	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid		544

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
145	**		3-(2-cyclohexyl-6-quinolinyl)-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid		463
146	**		2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid		502
147	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-cyclohexyl-6-quinolinyl)propanoic acid		451
148	**		3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid		531
149	**		3-(2-bicyclo[2.2.1]hept-5-en-2-yl-6-quinolinyl)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid		525
150	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(1-phenylethyl)-6-quinolinyl]propanoic acid		537
151	**		3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid		595
152	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid		529
153	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid		559
154	**		2-[(2,6-difluorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid		493
155	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid		475
156	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,3-dimethoxyphenyl)-6-quinolinyl]propanoic acid		505

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
157	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid		539
158	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,3-dimethoxyphenyl)-6-quinolinyl]propanoic acid		569
159	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid		569
160	**		2-{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid		492
161	**		2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid		533
162	**		2-[(2,6-dichlorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid		543
163	**		3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)propanoic acid		551
164	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid		567
165	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid		577
166	**		3-[2-(2,4-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid		525
167	**		3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid		509
168	**		2-[(2,6-dimethoxybenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid		525

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
169	**		2-[(2,6-difluorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid		511
170	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-mesityl-6-quinolinyl)propanoic acid		487
171	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid		513
172	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-(2-mesityl-6-quinolinyl)propanoic acid		551
173	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid		577
174	**		2-{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid		500
175	**		2-{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]propanoic acid		484
176	**		3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}-2-[(2,6-dichlorobenzoyl)amino]propanoic acid		571
177	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid		493
178	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,3-difluorophenyl)-6-quinolinyl]propanoic acid		605
179	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid		579
180	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid		527

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
181	**		2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid		537
182	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid		551
183	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid		473
184	**		2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid		615
185	2S	Pure	(2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid		537
186	**		2-{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid		512
190	**		2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-pyrrolidinyl)-6-quinolinyl]propanoic acid		451
191	**		2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid		501
192	**		3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid		544
193	**		2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid		535
194	**		3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid		536
195	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid		481

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
196	**		2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]propanoic acid		524
197	2	Rac	3-[2-(4-chlorophenoxy)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid		515/517/519
198	2	Rac	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino}propanoic acid		498/500/502
199	2	Rac	methyl 2-amino-3-(2-phenyl-6-quinolinyl)propanoate		479
208	2	Rac	2-amino-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid hydrochloride		352
209	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate		538/540/542
210	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid		524/526/528
211	2	Rac	2-amino-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid hydrochloride		396
212	2	Rac	methyl 2-amino-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoate hydrochloride		410
213	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoate		548
214	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoic acid		532/534/536
215	A-2§	Pure	(-)-methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate	-34.60 (DMSO, 1 %)	538/540/542

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
216	B-2§	Pure	(+)-methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate	+33.88 (DMSO, 1 %)	538/540/542
217	A-2§	Pure	(-)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid	-23.95 (DMSO, 1 %)	524/526/528
218	B-2§	Pure	(+)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid	+26.10 (DMSO, 1 %)	524/526/528
219	2,2S	Mixt	3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid		589
220	2,2S	Mixt	methyl 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate		603
221	2,2S	Mixt	methyl 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-methylpyrrolidinyl]carbonyl}amino)propanoate		477
222	2S	Pure	methyl (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	ee : 93 %	562/564/566
223	1R,3S,1S	Pure	(1R,3S)-3-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1,2,2-trimethylcyclopentanecarboxylic acid	-3.89 (CH_3CN, 1 %)	557/559/561
224	2	Rac	2-{[(6-amino-3-pyridinyl]carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		481/483/485
225	2S	Pure	methyl (2S)-2-{[(2-amino-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	ee : 93 %	495/497/499
226	2S	Pure	(2S)-2-{[(2-amino-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	-36.89 (DMSO, 1 %)	481/483/485

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
227	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]propanoic acid		511/513/515
228	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate		539/541/543
229	3S,1R,1S	Pure	(1R,3S)-3-[({[(1S)-1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl]amino}carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid	+31.54 (THF, 1 %)	543/545/547
230	2S,4R	Pure	(2S)-2-({[(4R)-3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	+34.67 (CH_3OH, 1 %)	550/552/554
231	2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[2-(1-piperidinyl)benzoyl]amino}propanoate	+37.73 (CH_3OH, 1 %)	562/564/566
232	2S,3	Mixt	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(4-{[(1,1-dioxidotetrahydro-3-thienyl)amino]methyl}benzoyl)amino]propanoate		626/628/630
233	2S	Pure	(2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	-62.43 (CH_3OH, 1 %)	548/550/552/554
234	2S	Pure	methyl (2S)-2-{[(2-chloro-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	+39.33 (CH_2Cl_2, 1%)	514/516/518/520
235	2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[2-(1-piperidinyl)benzoyl]amino}propanoic acid	+30,44 (DMSO, 1 %)	548/550/552
236	2S,3	Mixt	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(4-{[(1,1-dioxidotetrahydro-3-thienyl)amino]methyl}benzoyl)amino]propanoic acid		612/614/616
237	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]propanoate		555

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
238	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]propanoic acid		541/543
239	2	Rac	methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]propanoate		563
240	2S	Pure	(2S)-2-{[(2-chloro-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	-39.16 (CH_3OH, 1 %)	500/502/504
241	2S	Pure	methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate	+16.37 (CH_2Cl_2, 1 %)	539/541/543
242	2R	Pure	methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate	-17.04 (CH_2Cl_2, 1 %)	539/541/543
243	2S	Pure	methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoate	+3.00 (CH_2Cl_2, 1 %)	507/509/511
244	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid	-32.15 (DMSO, 1 %)	525/527/529
245	2R	Pure	(2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid	+31.40 (DMSO, 1 %)	525/527/529
246	2R,2S	Pure	methyl (2R)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate	-29.51 (CH_2Cl_2, 1 %)	479
247	2S,2R	Pure	methyl (2S)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate	+31.59 (CH_2Cl_2, 1 %)	479
248	2S,2S	Pure	methyl (2S)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate	+32.42 (CH_2Cl_2, 1%)	479
249	2R,2R	Pure	methyl (2R)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate	-33.11 (CH_2Cl_2, 1 %)	479

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
250	2R,2S	Pure	(2R)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	-63.77 (CH_2Cl_2, 1 %)	465
251	2S,2R	Pure	(2S)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	+65.72 (CH2Cl2, 1 %)	465
252	2S,2S	Pure	(2S)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	+51.10 (CH_2Cl_2, 1 %)	465
253	2R,2R	Pure	(2R)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	-57.31 (CH_2Cl_2, 1 %)	465
254	2R,4R	Pure	methyl (2R)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate	-20.52 (CH_2Cl_2, 1 %)	524
255	2R,4R	Pure	(2R)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid	ee: 100 %	510
256	2	Rac	2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]propanoic acid		549/551/553
257	2	Rac	methyl 3-[(2,6-dichlorophenyl)amino]-2-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-3-oxopropanoate		547/549/551
258	2	Rac	methyl 2-[({1-[(tert-butoxycarbonyl)amino]cyclopentyl} carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		586/588/590
259	2	Rac	methyl 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		486/488/490
260	2	Rac	2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid		472/474/476
261	1S	Pure	tert-butyl 4-(4-{[({(1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl}amino)carbonyl]benzyl}-1-piperidinecarboxylate	-74 (MeOH, 1 %)	676/678/680

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
262	2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[4-(4-piperidinylmethyl)benzoyl]amino}propanoate		576/578/580
263	2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[4-(4-piperidinylmethyl)benzoyl]amino}propanoic acid	-20.46 (DMSO, 1 %)	562/564/566
264	2	Rac	tert-butyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate		589/591/593 /595/597
265	2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(4,6-dimethoxy-1,3,5-triazin-2-yl)amino]propanoate	-3.93 (CH_3OH, 1 %)	514/516/518
266	2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-{[3-(4-piperidinyl)benzoyl]amino}propanoic acid	-7.93 (DMSO, 1 %)	548/550/552
267	2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(4,6-dimethoxy-1,3,5-triazin-2-yl)amino]propanoic acid	+67.53 (DMSO, 1 %)	500/502
268	2S	Pure	methyl (2S)-2-{[2-(4-chlorophenyl)-2-methylpropanoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate	ee: 93 %	555/557/559
269	2S (95 %) 2R (5 %)	Mixt	(2S)-2-{[2-(4-chlorophenyl)-2-methylpropanoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid (95 %) (2R)-2-{[2-(4-chlorophenyl)-2-methylpropanoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid (5 %)	ee: 90 %	541/543/545
270	2S (95 %) 2R (5 %)	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-methyl-2-phenylpropanoyl)amino]propanoic acid (95 %) (2R)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-methyl-2-phenylpropanoyl)amino]propanoic acid (5 %)	ee: 90 %	507/509/511
271	2S	Pure	methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2-methyl-2-phenylpropanoyl)amino]propanoate	ee: 94 %	521/523/525

n°	Configuration data		IUPAC Name	α_D (25 °C) or ee	LC-MS (MH^+)
272	2S	Pure	(2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({1-[2-(diethylamino)ethyl]cyclopentyl}carbonyl)amino]propanoic acid	+26.81 (CH3OH, 1 %)	556/558/560
273	2S	Pure	(2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid	ee: 100 %	534/536
274	2S,2R	Pure	(2S)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid	+17.58 (CH_3OH, 1 %)	474/476/478
275	2,2S	Mixt	methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate		612/614/616
276	2S	Pure	methyl (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate	-49.28 (DMSO, 1 %)	582/584/586
277	2S	Pure	(2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid	-43 (DMSO, 1 %)	568/570/572
278	2S,2S	Pure	(2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid	+5.77 (CH_3OH, 1 %)	562/564/566
279	2,2S	Mixt	3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid		598/600/602
282	1	Rac	2,6-dichloro-N-{1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-[(methylsulfonyl)amino]-2-oxoethyl}benzamide		610/612/614

** compounds synthesised from the corresponding "L" amino acid. The stereochemistry was not determined; the carbon ator to which R^2 and R^3 are attached could be in the "S" or "R" configuration, with a proportion of 2S isomer comprised between 50 % and 100 %.

Example 6: In vitro biological assay. U937 / VCAM-1 adhesion assay.

Compounds of the invention are tested in a VLA-4 dependent adhesion test.

The VLA-4 expressing cell line U937 (ATCC n°: CRL 1593) is cultured in RPMI 1640 medium supplemented with foetal bovine serum 10 %. Prior to the assay cells are washed, resuspended in HBSS BSA 0.1 % at $5x10^6$ cells/ml and loaded with the fluorescent dye Calcein-AM at a final concentration of 10 µmol/l for 15 min at 37 °C. After washing, cells are resuspended in RPMI at $2x10^6$ cells/ml.

96 well microtiter plates are coated with 50 µl aliquots of soluble human recombinant VCAM-1 (2.5 µg/ml in DPBS) overnight at 4 °C. DPBS alone is added to some wells for non specific adhesion measurement. Wells are washed to remove unbound protein and blocked by incubation with 1 % BSA for 1 h at 37 °C to reduce background adherence.

Compounds dissolved in DMSO are diluted in RPMI HEPES (25 mmol/l) and added to the wells in a 50 µl volume. Final DMSO concentration is 1 %. Vehicle alone is added to control wells. Calcein loaded cells are then plated in 50 µl volume and the plates are incubated for 45 min at room temperature.

Fluorescence is measured using the Cytofluor plate reader (excitation:485 nm; emission: 530 nm).

Plates are washed 4 times to remove non-adherent cells and fluorescence was read again.

The percentage of cell adhesion is calculated as: fluorescence of adherent cells/ fluorescence of total cells x 100 (F_X%). Nonspecific adhesion is calculated from DPBS wells (F_{ns}%). Specific adhesion is : F_X% - F_{ns}%.

Adhesion inhibition is calculated as the decrease of the adhesion of treated cells compared to the adhesion of control cells and expressed in percent as: $100 - [(F_X\% - F_{ns}\%) / (F_C\% - F_{ns}\%) \times 100]$.

IC_{50} is evaluated from a dose-response curve using the following equation:

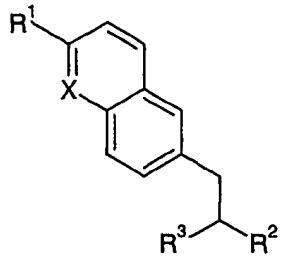
$Y= A + ((B-A)/ (1 + ((C / X)^D)))$

with A = minimum inhibition, B = maximum inhibition, C = IC_{50} and D = Hill slope.

Preferred compounds of the invention inhibit the U937 adhesion to VCAM with IC_{50} values below 1 µmol/l.

CLAIMS

1. Compound having the formula I or a pharmaceutically acceptable salt thereof,

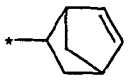


(I)

wherein

X is N or CH;

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or an oxy derivative, or a group of formula:

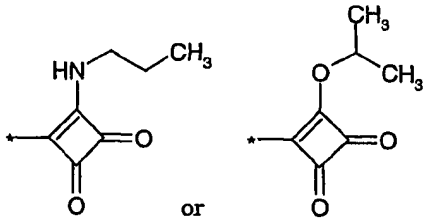


;

R^2 is $-NR^4R^5$, $-OR^4$ or $-C(=O)NR^5R^6$;

R^3 is tetrazole, -CN, $-CH_2OH$ or $-CO-R^7$;

R^4 is H, $-G^1-R^8$, or a group of formula:



;

R^5 is H, C1-4-alkyl; or $-NR^4R^5$ represents an heterocycle or $-N=CR^9R^{10}$;

R^6 is aryl, heterocycle, cycloalkyl or aralkyl;

R^7 is hydroxy, amino, hydroxylamino, an oxy derivative or an amino derivative;

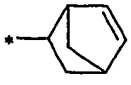
G^1 is CO, CH_2, SO_2;

R^8 is aryl, heterocycle, cycloalkyl, aralkyl or -NH-aryl;

R^9 is aryl; and

R^{10} is ether;

with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:



; and

with the proviso that, when X is CH, R^1 is cycloalkyl, R^2 is $-NR^4R^5$, R^3 is $-CO-R^7$, R^4 is H or $-G^1-R^8$, R^5 is H, C1-4-alkyl, G^1 is CO, CH_2, SO_2, R^8 is an optionally substituted phenyl, cycloalkyl or -NH-phenyl (an optionally substituted), then R^7 is neither an oxy derivative of formula $-O-CHR^bR^c$ wherein R^b is H, C1-6-alkyl or an optionally substituted phenyl and R^c is an optionally substituted phenyl, nor an amino derivative of formula $-NR^d-CHR^bR^c$ wherein R^b and R^c have the same definitions as described above, and R^d is H or C1-6-alkyl.

2. A compound according to claim 1, wherein
R^1 is cycloalkyl, aryl, aromatic heterocycle or aralkyl;
R^2 is $-NR^4R^5$;
R^3 is $-CO-R^7$;
R^4 is $-G^1-R^8$;
R^5 is H, or C1-4-alkyl;
R^7 is hydroxy, amino, hydroxylamino or an oxy derivative;
G^1 is CO; and
R^8 is aryl, heterocycle, cycloalkyl or -NH-aryl.

3. A compound according to claim 2, wherein
R^1 is 2,6-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dimethoxyphenyl, 2-nitrophenyl, 2-(trifluoromethyl)phenyl, 2-bromophenyl, 2-(1,3-benzodioxol-5-yl)-1-methylethyl, 2-methoxyphenyl, 4-(methylsulfonyl)phenyl, 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl, 2,6-dimethylphenyl, 2-chloro-6-nitrophenyl, 3,5-dichloro-4-pyridinyl, 2-chloro-6-fluorophenyl, 2-methoxy-1-naphthyl, 2-mesityl;
R^2 is $-NHR^4$, wherein R^4 is $-G^1-R^8$;
R^7 is hydroxy, amino or C1-4-alkyloxy;
G^1 is CO; and
R^8 is 2,6-dichlorophenyl, 1-carboxy-1,2,2-trimethyl-3-cyclopentyl, 1-[(4-methylphenyl)sulfonyl)-2-piperidinyl, 1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl, 1-(4-chlorophenyl)cyclopentyl, 2-chloro-4-(methylsulfonyl)phenyl, 2-chloro-6-methylphenyl, 3-acetyl-1,3 thiazolidin-4-yl, 2,6-dimethoxyphenyl, 2,6-dimethylphenyl, 2,6-difluorophenyl, 2-chloro-4-(methylsulfonyl)phenyl, 1-(methylsulfonyl)-2-piperidinyl, 2-methyltetrahydro-2-furanyl, 1-acetyl-2-pyrrolidinyl, 1-(phenylsulfonyl)-2-pyrrolidinyl, 2,4-dichloro-6-methyl-3-pyridinyl, 1-benzyl-5-oxo-2-pyrrolidinyl, 3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl or 1-[2-

(diethylamino)ethyl]cyclopentyl.

4. A compound according to claim 3, wherein
R^1 is 2,6-dichlorophenyl, 2,6-dimethoxyphenyl, 3,5-dichloro-4-pyridinyl, 2-nitrophenyl, 2-chloro-6-fluorophenyl, 2-methoxy-1-naphthyl or 2-chloro-6-nitrophenyl;
R^2 is -NH-C(=O)-R^8;
R^7 is hydroxy or C1-4-alkyloxy; and
R^8 is 2,6-dichlorophenyl, 1-carboxy-1,2,2-trimethyl-3-cyclopentyl , 1-((4-methylphenyl)sulfonyl)-2-piperidinyl, 1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl, 1-(4-chlorophenyl)cyclopentyl, 2-chloro-4-(methylsulfonyl)phenyl, 2-chloro-6-methylphenyl, 1-(phenylsulfonyl)-2-pyrrolidinyl, 2,4-dichloro-6-methyl-3-pyridinyl or 1-benzyl-5-oxo-2-pyrrolidinyl.

5. A compound according to any of claims 1 to 4, wherein, when the carbon atom to which R^2 and R^3 are attached is asymmetric, it is in the "S"-configuration.

6. A compound according to claim 1 selected from the group consisting of methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethylbenzoyl)amino]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(4-pyridinyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[(2,6-difluorobenzoyl)amino]propanoic acid; methyl (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dichlorophenyl)-6-

quinolinyl]propanoic acid; 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; (1R,3S)-3-[({1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-difluorobenzoyl)amino]propanoic acid; (2S)-2-[(2,6-difluorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid; (2S)-2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-nitrophenyl]-6-quinolinyl}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; (2S)-3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(4R)-3-acetyl-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoate; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; 2,6-dichloro-N-[1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-(hydroxyamino)-2-oxoethyl]benzamide; N-(2-amino-1-{[2-

(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-oxoethyl)-2,6-dichlorobenzamide; methyl (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoate; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(methylsulfonyl)piperidinyl]carbonyl}amino)propanoic acid; ({2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoyl}oxy)methyl pivalate; 2-[(((2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-chlorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2-bromophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 3-[2-(2-bromophenyl)-6-quinolinyl]-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; 2-[({(2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-[2-(2-bromophenyl)-6-quinolinyl]propanoic acid; 3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}-2-[({(2S)-1-[(4-methylphenyl)sulfonyl]piperidinyl}carbonyl)amino]propanoic acid; 2-[(((2S,3aS,7aS)-1-[(4-methylphenyl)sulfonyl]octahydro-1H-indol-2-yl}carbonyl)amino]-3-{2-[2-chloro-5-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-cyclohexyl-6-quinolinyl)propanoic acid; 3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-[(2-chloro-6-methylbenzoyl)amino]propanoic acid; 3-{2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-quinolinyl}-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,3-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2-methoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,3-

dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid; 3-[2-(2-chloro-6-fluorophenyl)-6-quinolinyl]-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 3-[2-(2,4-dichlorophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-{2-[2-(trifluoromethyl)phenyl]-6-quinolinyl}propanoic acid; 2-[(2,6-difluorobenzoyl)amino]-3-{2-[4-(methylsulfonyl)phenyl]-6-quinolinyl}propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-(2-mesityl-6-quinolinyl)propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-(2-mesityl-6-quinolinyl)propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; 2-{[(1-acetyl-2-pyrrolidinyl)carbonyl]amino}-3-[2-(2,4-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid; 2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(2,3-difluorophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dimethoxybenzoyl)amino]-3-[2-(2-methoxy-1-naphthyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid; 2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-{2-[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-6-quinolinyl}propanoic acid; (2S)-2-{[2-chloro-4-(methylsulfonyl)benzoyl]amino}-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid; 3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dichlorobenzoyl)amino]propanoic acid; 3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]-2-[(2,6-dimethoxybenzoyl)amino]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2,6-difluorophenyl)-6-quinolinyl]propanoic acid; 2-[(2-chloro-6-methylbenzoyl)amino]-3-[2-(2-chloro-6-nitrophenyl)-6-quinolinyl]propanoic acid; 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; (-)-methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate; (-)-2-

[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; (+)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid; 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid; methyl 3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate; methyl (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; (1R,3S)-3-{[((1S)-1-{[2-(2,6-dichlorophenyl)-6-quinolinyl]methyl}-2-methoxy-2-oxoethyl)amino]carbonyl}-1,2,2-trimethylcyclopentanecarboxylic acid; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; (1R,3S)-3-[(((1S)-1-carboxy-2-[2-(2,6-dichlorophenyl)-6-quinolinyl]ethyl}amino)carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid; (2S)-2-({[(4R)-3-acetyl-1,1-dioxido-1,3-thiazolidin-4-yl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-{[(2,4-dichloro-6-methyl-3-pyridinyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoate; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; 2-{[(1-aminocyclopentyl)carbonyl]amino}-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-[((1-[2-(diethylamino)ethyl]cyclopentyl}carbonyl)amino]propanoic acid; (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]-2-({[(2R)-2-methyltetrahydro-2-furanyl]carbonyl}amino)propanoic acid; methyl 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoate; methyl (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; (2S)-2-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic

acid and 3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-({[(2S)-1-(phenylsulfonyl)pyrrolidinyl]carbonyl}amino)propanoic acid.

7. A compound selected from the group consisting of (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid; (2S)-2-({[(2S)-1-benzyl-5-oxopyrrolidinyl]carbonyl}amino)-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoic acid and (-)-2-[(2,6-dichlorobenzoyl)amino]-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoic acid.

8. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound according to any of claims 1 to 7 and a pharmaceutically acceptable adjuvant, diluent or carrier.

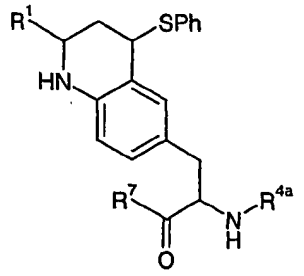
9. A compound according to any of claims 1 to 7 for use as a medicine.

10. Use of a compound according to any of claims 1 to 7 in the manufacture of a medicament.

11. Use of a compound according to any of claims 1 to 7 in the manufacture of a medicament for the treatment of VLA-4 dependent inflammatory diseases.

12. Use according to claim 10 for the manufacture of a medicament for the treatment of asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, inflammatory skin disorders including dermatitis, psoriasis, urticaria, pruritus and eczema, rheumatoid arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, multiple sclerosis and other autoimmune disorders, and atherosclerosis.

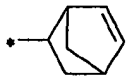
13. Synthesis intermediates of formula II,



II

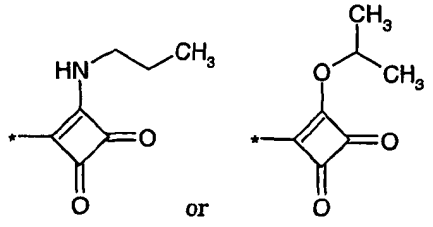
wherein

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or a group of formula:


;

R^{4a} is R^4 or P;

R^4 is H, $-G^1-R^8$ or a group of formula:



;

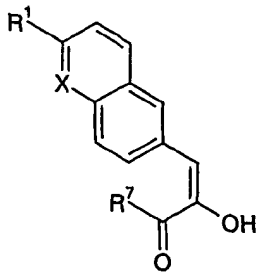
R^7 is hydroxy or an oxy derivative;

G^1 is CO, CH_2, SO_2;

R^8 is aryl, heterocycle, cycloalkyl, aralkyl or -NH-aryl; and

P is an amine protecting group.

14. Synthesis intermediates of formula III

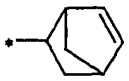


III

wherein

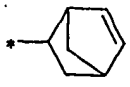
X is N or CH;

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or an oxy derivative, or a group of formula:

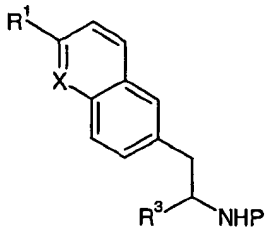

; and

R^7 is hydroxy or an oxy derivative;

with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:


.

15. Synthesis intermediates of formula IV

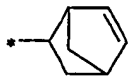


IV

wherein

X is N or CH;

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or an oxy derivative, or a group of formula:



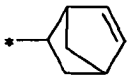
;

R^3 is -CO-R^7 ;

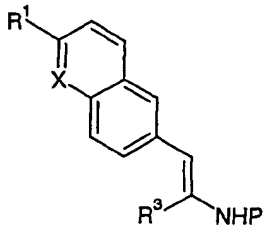
R^7 is hydroxy or an oxy derivative; and

P is an amine protecting group,

with the proviso that when X is CH, then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl or a group of formula:



16. Synthesis intermediates of formula VI

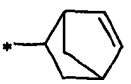


VI

wherein

X is N or CH;

R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or an oxy derivative, or a group of formula:



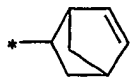
;

R^3 is -CO-R^7;

R^7 is hydroxy or an oxy derivative; and

P is an amine protecting group

with the proviso that when X is CH then R^1 is cycloalkyl, aryl, heterocycle, aralkyl, heterocycle-alkyl, or a group of formula:



17. Synthesis intermediates selected from the group consisting of methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-(benzoylamino)-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[4-(phenylsulfanyl)-2-(1,3-thiazol-2-yl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-[4-(phenylsulfanyl)-2-(4-pyridinyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2R)-2-[(2,6-dichlorobenzoyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethylphenyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-4-(phenylsulfanyl)-1,2,3,4-tetrahydro-6-quinolinyl]propanoate; methyl 3-[2-(2,6-

dichlorophenyl)-6-quinolinyl]-2-hydroxy-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenyl-6-quinolinyl)propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl)propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(4-chlorophenoxy)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-methoxy-6-quinolinyl)propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethylphenyl)-6-quinolinyl]propanoate; methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[2-(3,5-dichloro-4-pyridinyl)-6-quinolinyl]propanoate; methyl 2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]propanoate; ethyl 2-(acetylamino)-3-[6-(2,6-dichlorophenyl)-2-naphthyl]propanoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-phenoxy-6-quinolinyl)-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(4-chlorophenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-(2-methoxy-6-quinolinyl)-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2-methoxyphenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dimethoxyphenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenoxy)-6-quinolinyl]-2-propenoate; methyl 2-[(tert-butoxycarbonyl)amino]-3-[2-(2,6-dichlorophenyl)-6-quinolinyl]-2-propenoate; methyl (2-(acetylamino)-3-[6-(2,6-dimethoxyphenyl)-2-naphthyl]-2-propenoate; methyl 2-[(2,6-dichlorobenzoyl)amino]-3-(4-nitrophenyl)propanoate; methyl 2-[(2,6-dichlorobenzyl)amino]-3-(4-nitrophenyl)propanoate; methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzoyl)amino]propanoate; methyl 3-(4-aminophenyl)-2-[(2,6-dichlorobenzyl)amino]propanoate; 6-(benzyloxy)-2-chloroquinoline; 6-(benzyloxy)-2-phenoxyquinoline; 6-(benzyloxy)-2-(4-chlorophenoxy)quinoline; 6-(benzyloxy)-2-methoxyquinoline; 6-(benzyloxy)-2-(2-methoxyphenoxy)quinoline; 6-(benzyloxy)-2-(2,6-dimethoxyphenoxy)quinoline; 6-(benzyloxy)-2-(2,6-dichlorophenoxy)quinoline; 2-phenoxy-

6-quinolinol; 2-(4-chlorophenoxy)-6-quinolinol; 2-methoxy-6-quinolinol; 2-(2-methoxyphenoxy)-6-quinolinol; 2-(2,6-dimethoxyphenoxy)-6-quinolinol; 2-(2,6-dichlorophenoxy)-6-quinolinol; 2-phenoxy-6-quinolinyl trifluoromethanesulfonate; 2-(4-chlorophenoxy)-6-quinolinyl trifluoromethanesulfonate; 2-methoxy-6-quinolinyl trifluoromethanesulfonate; 2-(2-methoxyphenoxy)-6-quinolinyl trifluoromethanesulfonate; 2-(2,6-dimethoxyphenoxy)-6-quinolinyl trifluoromethanesulfonate; 2-(2,6-dichlorophenoxy)-6-quinolinyl trifluoromethanesulfonate; 6-(benzyloxy)-2-(2,6-dichlorophenyl)quinoline; 2-(2,6-dichlorophenyl)-6-quinolinol; 2-(2,6-dichlorophenyl)-6-quinolinyl trifluoromethanesulfonate; 2-(benzyloxy)-6-(2,6-dimethoxyphenyl)naphthalene; 6-(2,6-dimethoxyphenyl)-2-naphthol and 6-(2,6-dimethoxyphenyl)-2-naphthyl trifluoromethanesulfonate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03909

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/14 A61K31/47 C07D215/22 C07D401/06 C07D401/12
C07D215/36 C07C233/87 A61P37/08 A61P19/02 A61P29/00
C07C205/49 C07C237/36 C07C43/205 C07C309/65 C07C229/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VELA, MARCO A. ET AL: "Syntheses of 1- and 2-naphthol analogs of DL-tyrosine. Potential fluorescent probes of peptide structure and dynamics in complex environments" J. ORG. CHEM. (1990), 55(9), 2913-18, XP001096510 * scheme II * page 2914 ---	1,15,16
A	WO 00 66572 A (REDDY'S RESEARCH FOUNDATION, INDIA) 9 November 2000 (2000-11-09) examples 12,43,44 ---	1
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2003	22/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, J-C

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03909

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 798 291 A (SANTEN PHARMACEUTICAL CO., LTD., JAPAN) 1 October 1997 (1997-10-01) page 16; example 4 page 31; examples 6-2,6-3	1,15
A	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 07, 31 July 1997 (1997-07-31) & JP 09 087291 A (WAKAMOTO PHARMACEUT CO LTD), 31 March 1997 (1997-03-31) * 2-Naphthalenepropanoic acid,.alpha.-amino-6-methoxy-,phenylmethyl ester 2-Naphthalenepropanoic acid,.alpha.-(acetylamino)-6-methoxy- " * formula II * abstract	1,15
A	WO 99 10312 A (HOFFMANN LA ROCHE) 4 March 1999 (1999-03-04) the whole document	1-17
A	WO 00 15612 A (COMMERCON ALAIN ;BOURZAT JEAN DOMINIQUE (FR); FILOCHE BRUNO JACQUE) 23 March 2000 (2000-03-23) cited in the application the whole document	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/03909

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0066572 A	09-11-2000	AU 3983100 A	17-11-2000
		BG 106146 A	31-05-2002
		CA 2371757 A1	09-11-2000
		CN 1353699 T	12-06-2002
		CZ 20013832 A3	17-04-2002
		EE 200100540 A	16-12-2002
		EP 1175412 A1	30-01-2002
		HR 20010785 A1	28-02-2003
		WO 0066572 A1	09-11-2000
		JP 2002543194 T	17-12-2002
		NO 20015259 A	15-11-2001
		SK 15092001 A3	09-05-2002
		TR 200103848 T2	22-04-2002
EP 0798291 A	01-10-1997	DE 69528197 D1	17-10-2002
		DE 69528197 T2	05-06-2003
		EP 0798291 A1	01-10-1997
		US 5968980 A	19-10-1999
		WO 9618606 A1	20-06-1996
		JP 2920741 B2	19-07-1999
		JP 8231492 A	10-09-1996
JP 09087291 A	31-03-1997	NONE	
WO 9910312 A	04-03-1999	AU 739511 B2	11-10-2001
		AU 9262098 A	16-03-1999
		BR 9811730 A	05-09-2000
		CA 2301377 A1	04-03-1999
		CN 1281430 T	24-01-2001
		WO 9910312 A1	04-03-1999
		EP 1005445 A1	07-06-2000
		HR 20000080 A1	31-12-2000
		HU 0003642 A2	28-02-2001
		JP 2001514162 T	11-09-2001
		NO 20000841 A	21-02-2000
		NZ 502813 A	25-10-2002
		PL 338857 A1	20-11-2000
		TR 200000482 T2	21-06-2000
		TW 490458 B	11-06-2002
		US 6229011 B1	08-05-2001
		ZA 9807604 A	18-05-1999
WO 0015612 A	23-03-2000	AU 754557 B2	21-11-2002
		AU 5634399 A	03-04-2000
		BR 9913222 A	16-10-2001
		CA 2341677 A1	23-03-2000
		CN 1323295 T	21-11-2001
		EP 1114028 A1	11-07-2001
		WO 0015612 A1	23-03-2000
		HU 0104766 A2	29-04-2002
		JP 2002524552 T	06-08-2002
		NO 20010942 A	19-04-2001
		NZ 509781 A	30-05-2003
		PL 346248 A1	28-01-2002
		SK 2612001 A3	06-11-2001
		TR 200100588 T2	21-08-2001
		US 6608084 B1	19-08-2003
		ZA 200101259 A	06-02-2002